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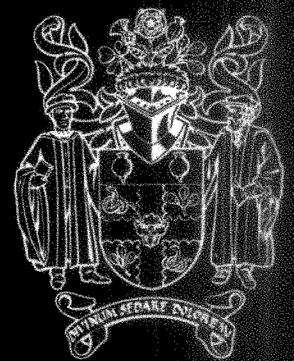

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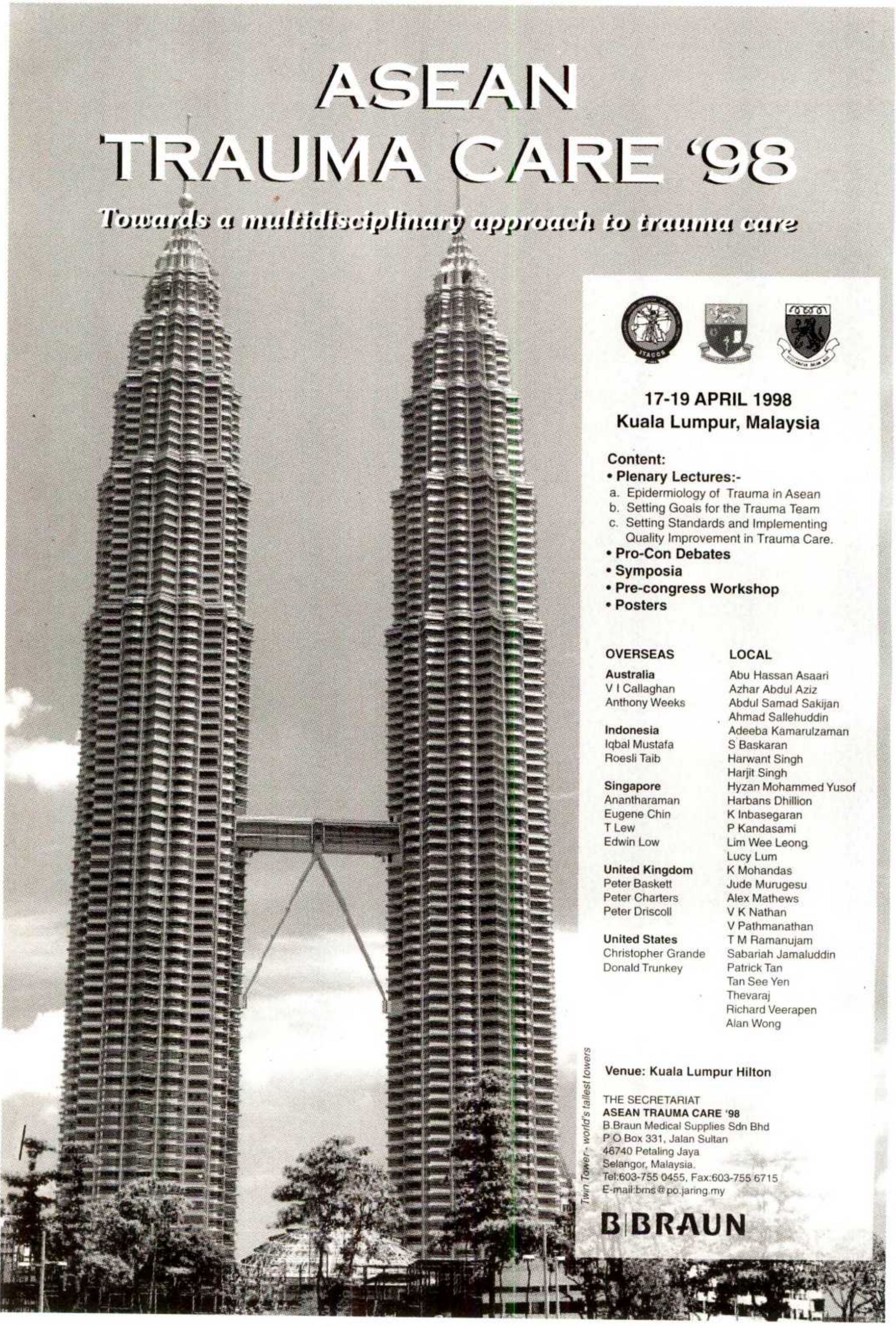

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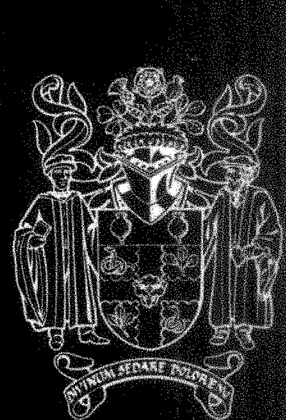

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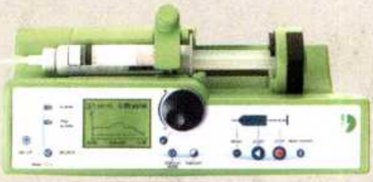

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EPIDEMIOLOGY IN ANAESTHESIA AND INTENSIVE CARE

A.1 Abdominal aortic surgery: cardiac enlargement on preoperative chest x-ray as an independent predictor of postoperative left ventricular failure

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Introduction: Lowered LVEF is a predictor of post operative LVF during AAS (1) Although a radiologic cardio-thoracic ratio (CTR) > 0 5 indicates LVEF < 40% in as much as 70% of coronary artery-diseaded (CAD) patients only Foster et al (2) demonstrated an association between preoperative CTR and post operative LVF The aim of our study was to evaluate several preoperative classical predictors and variables, including CTR, in prediction of LVF after AAS

Materials and Methods: During a 52 months period, 223 consecutive patients undergoing planed AAS were prospectively studied. In every case we noted age, previous myocardial infarction (MI), previous episod of acute LVF, CTR > 0 5 or not, regional hypokinesia on TTE, gated nucleide LVEF < 50% or not In case of persistent LVF surgery was delayed Both anaesthesia, per and post operative monitoring with Swan-ganz catheter and ST segment monitoring, agressive treatment of hemodynamic abnormalities and ischemia, post operative ventilation and analgesia, were standardized LVF was defined by clinical and radiologic signs of pulmonary edema and either PAOP > 18 mmHg or sucessful response to diuretics and/or inotropic support Results were analyzed by univariate and multivariate analysis.

Results: Aortic clamping level was mainly infrarenal (93%) Post operative LVF occurred in 20 patients (8 8%) without any related death. Main results are given in the Table.

Preoperative variable	n with outcome and variable/n with variable	Univariate Analysis p value	Multivariate p value/OR
Age >65 yr	16/112	0 01	NS
Previous MI	4/29	NS	NS
Previous LVF	5/11	0 00001	0 0023/10 735
Goldman' score 3–4	10/54	0 0012	NS
Detsky' score 2 + 3	2/4	0 0003	NS
CTR > 0 5	11/51	0 0002	0 0197/3.718
Hypokinesia	8/45	NS	NS
LVEF < 50%	5/47	0 02	NS

Discussion, Conclusion: Our main adjunct is to show that, surprisingly, a simple and cheap preoperative sign, i.e CTR > 0 5, is one of the most powerful independant predictor of post operative LVF.

References

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A.2 Preoperative thallium imaging and coronary revascularization in critical limb ischaemia: impact on perioperative morbidity and long-term survival

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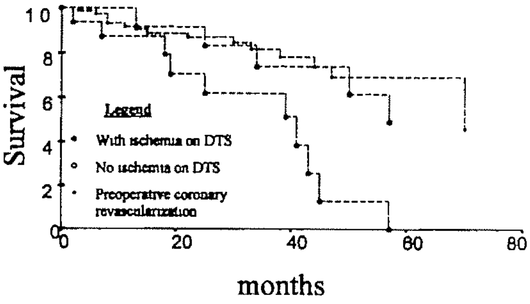
Background: The value of dipyridamole-thallium scanning (DTS) in predicting perioperative morbidity has been studied. Data on the effect of DTS and selective preoperative coronary revascularization (Cor-Rev) on long-term outcome, however, is lacking

Methods: 113 patients with critical lower limb ischemia scheduled for distal arterial bypass surgery underwent routine preoperative DTS. Patients with moderate-severe revesible defects on DTS had coronary catheterization and PTCA or CABG if indicated Their perioperative and long term morbidity and mortality were recorded

Results: 54 (47 8%) patients had history of heart disease, DTS was abnormal in 60 (53.1%), showing reversible ischemia in 49 (43.4%). Of 33 (29.2%) patients referred to coronary catheterization, 9 underwent PTCA and 4 had CABG without complications Surgery was performed in all but 2 patients; 2 (1.8%) died postoperatively, 3 (2 7%) sustained nonfatal postoperative MI and 2 had unstable angina None of the 13 patients with preoperative Cor-Rev had perioperative cardiac complication No clinical or DTS variable correlated with perioperative events. During follow-up (33.4 ± 2.2 months) 30 (28 0%) patients died Survival was lower with moderate-severe ischemia on DTS (40 ± 4 vs. 63 ± 4 months; $p < 0\,005$). Patients with preoperative Cor-Rev followed a survival curve similar to those without ischemia on DTS (61 ± 8 vs. 63 ± 4 months; NS) and significantly different from those with such defect without Cor-Rev (34 ± 5 months; $p < 0.017$)



Conclusion: In patients with critical limb ischemia, routine screening with DTS and selective preoperative coronary revascularization result in low perioperative cardiac morbidity and mortality and longer survival

A.3 Electrocardiographic and cardiokymography stress testing for cardiac risk assessment in patients undergoing non-cardiac surgery

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Background and Goal of Study: Preoperative risk stratification of patients with coronary artery disease (CAD) undergoing noncardiac surgery remains challenging (1). The value of preoperative stress cardiokymography (CKG) in predicting perioperative cardiac complications is still uncertain The goal of this study was to assess the predictive value of clinical variables, stress ECG and CKG

Materials and Methods: After obtaining institutional approval and informed consent 171 patients with definite CAD or at high risk for it scheduled for major elective noncardiac surgery were prospectively enrolled. All patients underwent preoperative bicycle ergometer testing with simultaneous measurements of ECG and CKG A 12-lead ECG and CK-MB- and Troponin-T-levels were obtained daily during the first five postoperative days. ECG and CKG analyses were performed by blinded investigators. A peri-operative cardiac complication was defined as myocardial infarction, prolonged myocardial ischaemia (Troponin T > 0 1 ng/ml or ST-depression ≥0 1 mV on at least two successive days), congestive heart failure or ventricular tachyarrhythmias. Potential univariate correlates of adverse outcomes were identified by Fisher's exact test.

Results and Discussion: 13 patients (7 6%) developed major perioperative cardiac complications myocardial infarction occurred in three and prolonged myocardial ischaemia in 10 patients. Definite CAD and exercise ECG were significant predictors of cardiac events (Tab) Although previous studies investigating CKG for diagnosis of CAD showed higher predictive accuracy for CKG compared to ECG (2), in our trial CKG was not predictive of perioperative cardiac complications However, combining clinical variables as definite CAD or specific types of surgery with positive ECG- and CKG-results increased the prediction of cardiac events to 34%, if three of these variables were present

Table Sensitivity (Sens), Specificity (Spec)

	Sens	Spec	Predictive value	p
CAD	92%	57%	15%	0 001
ECG	69%	73%	18%	0 03
CKG	77%	47%	11%	0 15

Conclusions: Stress ECG and definite CAD in contrast to CKG predicted cardiac events Combining clinical data with cardiac testing improved preoperative risk assessment and could limit needless investigations.

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A.4 Preoperative coronary angiography in patients undergoing abdominal aortic surgery: five years' experience

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Aim of the Study: to determine preoperative clinical parameters associated with the indication for preoperative coronary angiography (CA) in patients scheduled for abdominal aortic surgery (AAS) in the 1993–1997 period

Methods: 666 consecutive patients underwent CA based on the following indications angina pectoris or history of myocardial infarction (MI), age between 60 and 71 years and aneurysm procedure or age <71 and combined surgery (aorta and carotid, renal or mesenteric artery).

We retrospectively considered the decision to proceed or not to CA as justified when: 1) CA was performed and followed by coronary revascularization without cardiac complication after AAS. 2) CA was not performed and no cardiac complication (death, MI, heart failure) occurred after AAS.

We retrospectively rejected the decision when: 1) CA was not followed by revascularisation or the following revascularization was associated with cardiac complication. 2) CA was not performed and cardiac complication occurred after AAS. Odds ratio (OR) and their 95% confidence intervals (CI) were calculated.

Results: CA was performed in 302 patients. In 54 (18%) CA was followed by revascularization. Twelve patients (3%) presented severe cardiac complication (8 death) after AAS over the 364 patients without preoperative CA,. Using a multivariate analysis, age, type of aortic surgery (aneurysm versus occlusive aortic disease), combined surgery, serum creatinine >150 μmol/l hypertension, history of heart failure or atrial arrhythmia were not associated with justified CA. Preoperative predictive factors for justified CA are summarized in the table:

	OR [IC 95%]	P
Angina pectoris	3.22 [2.43–4.26]	0.0001
History of MI	2.8 [2.05–3.9]	0.001
History of revascularization	0.3 [0.18–0.5]	0.02
Diabetes	2.16 [1.46–3.19]	0.04
β-blockers	2.14 [1.76–2.86]	0.01

Conclusion: Preoperative CA should be performed in patients with clinical evidence of coronary artery disease or potential silent coronary artery disease (diabetes, β-blockers). Conversely, CA might not be performed in other cases especially in revascularized patients without recurrent angina pectoris

A.5 Hypertension and perioperative cardiovascular complications: meta-analysis of observational studies

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Background and Goal: Hypertension is often dismissed as a risk factor for preoperative cardiovascular complications because it does not appear in risk equations such as those of Goldman et al., and Larsen et al. (1, 2) We undertook a meta-analysis of observational studies of risk factors for perioperative cardiovascular complications to elucidate the role of hypertensive disease in this context.

Materials and Methods: Studies were identified by a search of the Medline database and by searching the reference lists of papers obtained from Medline and of relevant review papers. Studies were sought which gave information on the possible association between hypertensive disease and perioperative complications. The aim of this meta-analysis was to examine the effects of hypertensive disease and studies which defined hypertension solely in terms of an elevated admission blood pressure were excluded. Studies were included if the crude data on hypertension and the occurrence of complications could be extracted from the publication. For each study the crude odds ratio for the effect of hypertension and its variance were calculated. Fixed effects meta-analyses was performed using standard methods. (3) A statistical test for heterogeneity was also performed.

Results: Fourteen studies ranging in size from 60 to 2,609 patients were identified for inclusion in this meta-analysis. A total of 9,223 patients was included.

Using fixed effects meta-analysis, the pooled log odds ratio for the effect of hypertension was 0.44, giving the odds ratio of 1.55 (95% CI 1.29 to 1.87, $z = 4.63$, $p < 0.001$). The test for heterogeneity was not significant ($Q = 14.84$, $p = 0.32$ 13 df).

Conclusion: This meta-analysis demonstrates a significant association between hypertensive disease and perioperative cardiovascular complications.

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A.6 Laparoscopy *vs* laparotomy for cholecystectomy in elderly patients

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Background and Goal of Study: This study shows a particular usefulness of laparoscopic cholecystectomy in patients aged 70 or over in comparison with the standard laparotomy.

Materials and Methods: 110 patients ASA 2 and 3 scheduled for cholecystectomy were blindly randomized into 2 groups: laparotomy (n = 52) and laparoscopy (n = 58). All patients were premedicated orally with midazolam 7.5 mg and ondansetron 4 mg. Anaesthesia was indused with fentanyl, methoheksital, suxamethonium and after intubation maintained with 66% nitrous oxide in oxygen, and atracurium; on pain stimuli fentanyl was added. IPPV ventilation supplied patients with 10 ml/kg of tidal volume. The following data were analyzed: ASA, postoperative side-effects and complications, duration of surgery and length of stay in hospital. All the results are expressed as mean ± SD and a statistical analysis ($p < 0.05$ significant) was done using chi-square test.

Results: Age, weight, height and gender were similar between the groups.

	Laparoscopy	Laparotomy
Number of patients	58	52
Age (yrs) (ns)	76.7 ± 2.2	75.9 ± 2.1
ASA 3 ($p < 0.05$)	39 = 67.4%	24 = 46.1%
Time of operations (ns)	54′ ± 5′	47′ ± 4′
Days of stay in hospital ($p < 0.05$)	<1	9.1 ± 2.8
Required analgesics	tramadol 1 dose	opioides every 4–5 hrs
Complications	no (incl. 7 days observation)	yes

In the laparotomy group severe complications were observed (respiratory insufficiency 9 = 17.3%, myocardial infarction 4 = 7.7%, transient CNS episodes 1 = 1.9%) although haemo-dynamic parameters and haemoglobin saturation did not show any evidence of instability during anaesthesia.

Conclusions: Laparoscopy can be strongly recommended for cholecystectomy in the elderly since it reduces incidence of postoperative side-effects (is less painful) as well a severe complications and ensures less traumatic recovery.

A.7 Evaluation of Possum as a tool for quality assurance in an anaesthesiological ICU

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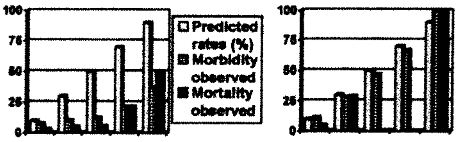
Background and Goal of Study: POSSUM is a Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. Aim of our study was to assess the predictive accuracy for morbidity and mortality as important outcome determinants in surgical patients.

Material and Methods: 207 patients were scored prospectively in our ICU after surgical procedures of 3 different clinics: Abdominal surgery, Urology and Traumatology. Evolving complications during intensive care treatment were documented as well as the length of stay in ICU and outcome. The predictive accuracy of POSSUM was assessed for each surgical department by the calculation of receiver operating characteristic (ROC) curves with determination of their area under curve (AUC). The mortality and morbidity predictor equations published by Copeland et al. [1] were applied to compare predicted deaths and complication rates with reported deaths and complication rates. A "Hannover" predictor equation was calculated on our data by logistic regression.

Results and Discussion: 41 patients developed complications (19.8%) and 12 died during their course in ICU (5.8%). Table 1 shows the calculated AUC data for each surgical department regarding morbidity and mortality:

Clinic	n	AUC morbidity	AUC mortality
Abd. Surgery	92	0.680	0.893
Urology	95	0.767	0.740
Traumatology	20	0.797	0.833
All patients	207	0.720	0.782

The Copeland predictor equations resulted in a lack of fit by overestimating the number of complications and deaths. They were adjusted by the "Hannover" predictor equations (Fig. 1):



These data show that prediction of morbidity and mortality is possible within a reasonable range.

Conclusion: POSSUM is applicable to patients from different surgical specialties and therefore appropriate for an anaesthesiological ICU. Risk adjustment has to be done, thereby managing to perform sequential analysis of morbidity and mortality rates as important factors for quality control.

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A.8 Development of a high dependency unit illness severity scoring system

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Introduction and Goal of Study: High dependency units (HDU's) have been developed to provide a level of care intermediate between the intensive care unit (ICU) and the general ward. Illness severity scoring systems such as APACHE II were developed for critically ill ICU patients (1). They require data from invasive monitoring, are complex and may be invalid for predominantly surgical HDU patients (2). This study outlines the development of a simple HDU scoring system

Method: Data, including chronic health status, were obtained from 220 surgical HDU patients. Pulse rate and non-invasive arterial pressure were combined into a simple table to give a two point cardiovascular assessment FiO2 and SpO2 were similarly combined to give three grades of respiratory status. Renal function was assessed from urine output. Data were analysed initially by univariable logistic regression against either survival or death within 14 days/transfer to ICU Variables found to be significant at the 5% level were include in a multivariable analysis to identify those factors independently related to outcome.

Results: The five acute variables below were shown to significantly affect outcome.

Variable	P value	Projected weighting
Albumin	p < 0 01	0–3
SpO2	p < 0.03	0–5
Renal	p < 0 01	0–6
Age >75 yrs	p < 0.07	0–2
CNS	p < 0.07	0–5

The relative impact on outcome and hence the projected weightings for the scoring system were obtained from the coefficient multivariable model Primary surgical diagnosis, chronic health status, cardiovascular status, temperature, Hb or WBC were not found to independently affect outcome.

Conclusion: We have developed a simple five point illness score for HDU patients requiring only basic physiological data. Further validation is in progress.

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A.9 Early prognosis value of SAPS II score after orthotopic liver transplantation

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Orthotopic Liver transplantation (OLT) is an heavy medico-surgical procedure regularly threatening the vital prognosis of receivers

To dispose of an objective vital score, we try to determine the accuracy of SAPS II (Simplified Acute Physiology Score), as an initial indicator of liver transplantation mortality.

Patients and Methods: 75 patients representing 82 OLT (50 male, 25 female) have been prospectively studied during a two year period SAPS II score was determined every day during three days after OLT: (SAPS 1, 2, 3).

In order to have a single value during the whole postoperative period, the sum of SAPS 1, 2, and 3 was calculated. (Σ).

Statistical analysis was performed with ANOVA. Results are expressed in mean ± sd, and $p < 0.05$ was considered significant.

Results: Global mortality during the study period was 18.5% (15 patients).

The difference between dead or alive patients with their SAPS scores are represented in Table 1

Table 1

	SAPS 1	SAPS 2	SAPS 3	Σ
Alive	24 ± 10	20 8 ± 11	19 2 ± 11	64 7 ± 30
Dead	38 6 ± 11	38 9 ± 14	37.1 ± 15	115 4 ± 39
p value	0 00007	0 00001	0.00001	0 0000001

Table 2 shows percent of survivor for each corresponding group of sum (Σ) value ($p = 0.000004$)

Table 2

Σ	<40	40–80	80–120	120–160	>160
% Survivor	100	90	70	30	0

Conclusions: SAPS II scores can be considered as good indicators of vital prognosis after OLT. Patients mortality shows significant variations according to the sum (Σ) value. These scores allow simple, quick and powerful determination of death risk in the early period after OLT.

References

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A.10 Using revised simplified acute physiology score (SAPS II) in patients admitted to a neurosurgical intensive care unit

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Background and Goal of Study: Prospectively acquired data from patients admitted in the neuro-surgical intensive care unit (NICU) were studied for evaluating the predictive accuracy of the revised Simplified Acute Physiology Score[1] (SAPS II) for outcome quality under the framework of quality assurance. SAPS II employs twelve physiological variables with additional weights for age, type of admission and three underlying diseases (AIDS, metastatic malignancies or hematological malignancy)

Materials and Methods: A six months survey for all patients staying more than 24 hours in the NICU and excluding all patients under sixteen years old Data on chosen demographic characteristics and specific physiological variables for SAPS II were collected within the 24 first hours of admission. Discharge vital status (dead or alive) and the length of NICU stay were recorded The Outcome parameters used were hospital mortality, the individual mortality risk computed directly from the SAPS II score, the standardized mortality index (SMI observed/predicted death rate with 99% confidence limits), and the ratio of actual to predicted length of stay in the NICU were used. Individual diagnostic categories were considered separately as subgroups. The Receiver operating characteristics curves (ROC) were obtained for SAPS II

Results and Discussion: SAPS II scoring was performed in a total of 387 patients. Forty-four (11.6%) patients (mean age 61 7) died in the NICU. For the whole group, the mean predicted mortality was 15%, and the mortality index 0 77. The mean SAPS II score for surviving patient was 24 points as compared with those who died (47 points) Stratifying SAPS score in different range and comparing with different diagnostic subgroups showed a significant correlation with the mortality rates and the estimated risk of death in the NICU (ROC 0 80–0.89). The mean length of NICU stay for survival patients was 11 days compared to 14 days for patients who died. There were indirect correlationship[2] between SAPS II score and the mean length of NICU stay.

Conclusions: The SAPS II scoring system was an accurate predictor of outcome in a NICU group and can be used for the control of quality assurance for these patients. Additional outcome and therapeutic scores (such as Glasgow coma scale, TISS and MPM) should be associated in order to optimize the quality of health care.

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A.11 Study of admissions for iatrogenic disease in a polyvalent intensive care unit

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Objectives: To evaluate the frequency and to determine the cause of serious iatrogenic accidents (drug-induced or related to a medical or surgical procedure) admitted to our Polyvalente Intensive Care Unit between 1991 and 1996

Methods: The files of all patients admitted to our unit during the study period were independently reviewed by two intensive care physicians. Definite or probable iatrogenic accidents were identified and classified according to their predictability, the possibility of prevention and a possible responsibility (medical, paramedical or none) The following data were compared to those of the general population admitted to the intensive Care Unit. age, sex, IGS, Mac Cabe, Omega, ventilation time and length of stay, number and nature of invasive treatments and mortality

Results: Of the 1,748 patients admitted during the study period, 71 (4 p.cent) were admitted for iatrogenic disease. This group was older (62 ± 17 versus 48 ± 20; $p < 0.0001$), with a more complicated medical history (Mac Cabe = 1 ± 1 versus 2 ± 1; $p < 0\ 0001$), less often ventilated (39 p.cent versus 51 p cent; $p = 0.05$), and more often treated by haemodialysis and haemofiltration (9 p.cent versus 21 p.cent; $p = 0.05$) than the general intensive care population. The iatrogenic accident prolonged the intensive care stay by an additional 421 days. It was fatal in 21 p.cent of cases It was predictable in 8 p cent of cases, and could have been prevented in 68 p.cent of cases. The physician was considered to be responsible in 62 p.cent of cases. The patient's origin had little influence of these parameters Drug-induced iatrogenic disease was more severe (IGS 2 = 42 ± 23 versus 28 ± 22, $p = 0.01$) and was accompanied by a longer stay than events related to medical or surgical procedures (7 ± 10 versus 3 ± 3, p = 0.002).

Conclusion: Iatrogenic accidents represent 4 p cent of intensive care admissions. They are responsible for an excess health expenditure, are largely predictable and could have been prevented in more than one half of cases

A.12 Head injury-induced haemostasis impairment

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Background and Goal of the Study: Head trauma has been associated with disseminated intravascular coagulation (DIC) Most of these events have been reported specially after opened head injury or when extra-cranial multiple injuries are associated. The aim of this study was to determine if closed head injury is able *per se* to induce DIC and the prognostic role of this DIC

Patients and Methods: 144 patients with head trauma associated or not to multiple injury were included in this retrospective study between January 1995 and December 1996 Sixteen patients were excluded from the study because haemostasis tests or clinical data collection was incomplete (n = 10), the diagnosis of DIC was equivocal (n = 2), because of anticoagulation prior to trauma (n = 1) or death occurring before coagulation test (n = 2) DIC was diagnosed on usual coagulation tests performed 2 2 H after trauma, including prothrombin time (PT < 70%), activated partial thromboplastin time (APTT > 1.3), fibrinogen levels (<1.5 g/l), platelet number (<150 G/l) and D-Dimers level >2 μg/ml, positive ethanol test and major decrease in factor V levels. Patients were classified in 2 groups whether head injury was associated to other multiple injuries (group B, n = 74) or not (group A, n = 55) The severity of injury was classified using the Acute Injury Score (AIS) separating head injury (AIS-head) from other injuries general)[1] Statistical analysis used exact Fisher's test Results are expressed as number of patients or as mean ± SEM, a p < 0.05 was considered significant

Results: Demographic data, time of first coagulation test and volume of perfusion were not different between the 2 groups. Twenty four patients developed DIC during the first 24 H: 4/55 in group A and 19/74 in group B. Erythrocytes were transfused in 2 group A patients and 14 group B patients with DIC. The higher the severity of head injury, the higher was the risk of developing DIC in group A (p = 0.008) and in group B (p < 0.001) (table I). Two of the four group A patients and 9/19 group B patients with DIC, whereas only 0/51 group A (p = 0.004) and 1/55 group B patients without DIC (p < 0.001), died or remained in chronic coma.

Discussion and Conclusion: This study confirms the association of severe head trauma with DIC because blood brain barrier disruption might allow cerebral tissue thromboplastin to enter into the systemic circulation and to trigger DIC. Despite the small number of patients, this study suggests that the occurrence of DIC is a marker of bad prognosis as suggested by the 50% incidence of death or chronic coma in patients with isolated severe (AIS > 2) head trauma with DIC as compared to 8.3% incidence of such events when DIC is absent. When multiple injury and DIC were present, death or chronic coma occurred in 47% of the patients and in only 1.8% in the absence of DIC. This preliminary study suggests the need of a prospective study to evaluate the risk associated to DIC after closed head trauma and questions the use of fresh frozen plasma in the early phase of trauma when cerebral injury may be aggravated by haemostasis impairment.

Table I

Head-AIS		1	2	3	4
Group A	• DIC+	0	0	2	2
	• DIC–	35	4	9	3
Group B	• DIC+	1	4	6	8
	• DIC–	36	10	5	4

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A.13 Perioperative silent myocardial ischaemia: an indicator of postoperative morbidity or mortality?

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Background and Goals: SMI occurs in around 31% of patients undergoing hip arthroplasty [1], is independent of the type of anaesthesia used [2] and may predict postoperative morbidity.

Materials and Methods: Patients undergoing major lower limb joint replacement surgery were studied. Past medical history and cardiac risk factors were recorded. Patients underwent ambulatory ECG monitoring (Holter) for 4 days perioperatively, starting on the preoperative night. Three months after discharge, patients were sent a questionnaire enquiring about new cardiorespiratory signs or symptoms. Results were analysed with the χ^2 and *t* tests.

Results and Discussion: 127 patients were studied – mean age 69.9 (SD8.5) years. 87 had risk factors for SMI. 42 patients had SMI perioperatively, 30 of whom had risk factors, the presence of risk factors did not predict the occurrence of SMI

The Mean (SEM) Ischaemic Load (IL) (Mins of SMI per hour monitored) for each day was *0.96* (0 43), *7.04* (2.2), *5.67* (1.54), and *2.64* (1 35) mins per hour. There were no differences between those with and without risk factors The overall ratio of postoperative to preoperative IL was 5.3.1, and the ratio for day 1 to day 3 postoperatively was 7 3 1 Again there was no clear difference between the IL of those with and those without risk factors. 123 responses to the questionnaire were received. There was one death due to bronchopneumonia. There was no difference in morbidity and mortality between those with risk factors and those without. There was an association at three months between new symptoms (chest pain, palpitations, breathlessness or fatigue) and both SMI (p < 0.01) and Ischaemic Load (p < 0.01). There was also an association between new or worsening fatigue and both SMI (p < 0 01) and Ischaemic Load (p < 0 001) New breathlessness was associated with new fatigue (p < 0.001).

Conclusions: The presence of cardiac risk factors did not predict the occurrence of SMI, or adverse cardiac outcome. However, perioperative SMI was associated with increasing postoperative fatigue. The increased SMI on the first postoperative night justifies nursing these patients in a high dependency unit.

Acknowledgements. This study was supported by the Wellcome Trust.

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A.14 Cardiac troponin I for diagnosis of postoperative myocardial infarction in cardiac surgery

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Postoperative myocardial infraction (PMI) is a major complication following cardiac surgery. The diagnosis may be difficult during the early postoperative period (1) Recent studies have shown that cardiac Troponin I (cTn1) is a highly specific marker of myocardial injury (2) The purpose of the study was to determine whether this assay is more specific and reliable than CKMB for the diagnosis of PMI

Materials and Methods: 265 patients scheduled for valve repair or replacement, coronary artery bypass surgery, or combined surgery were included

C Tn I was measured before cardiopulmonary bypass and 12 and 24 hours after (T12, T24). CKMB was measured on arrival in the ICU, and on the first postoperative day (POD1)

EKG was performed on arrival in the ICU and at least daily up to discharge. New ST segment changes, PMI (new Q waves, akinesia or severe hypokinesia), ventricular arrythmias were considered as postoperative adverse cardiac outcomes.

Results, mean ± SD are compared using Mann-Whitney test (* p < 0.05 significant). ROC curves have been established for cTn1 and CKMB.

Results: 8 patients developed a PMI, 15 ventricular arrythmias, and 26 new ST segment changes. Patients with PMI had a significantly higher cTnI level at T12 and T24 and higher CKMB at POD1 than patients without PMI. Patients with ST segment changes or ventricular arrythmias have also a significant increase in cTnI. Analysis of the ROC curves identified the best diagnosis values for cTn I and CKMB (T12 > 20 ng/ml, T24 > 36 ng/ml, CKMB > 74 UI/l) which indicates patients with a high probability of PMI. We found a 100% sensitivity for cTn1 at T12 and T24, and only 87% for CKMB at POD1. The best specificity was 93% for cTn1 at T24.

	All Patients	PMI (n = 8)	no PMI (n = 257)
T12	19 ± 27	86 15 ± 83 42*	17.92 ± 21 24
T24	16 ± 23	92 58 ± 28 95*	14 3 ± 18 49

Conclusion: C Tn I is more sensitive and specific than CKMB allowing an early and more reliable identification of patients with PMI.

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A.15 Postoperative troponin Ic cut-off value is reliable with early cardiac complications after aortic repair

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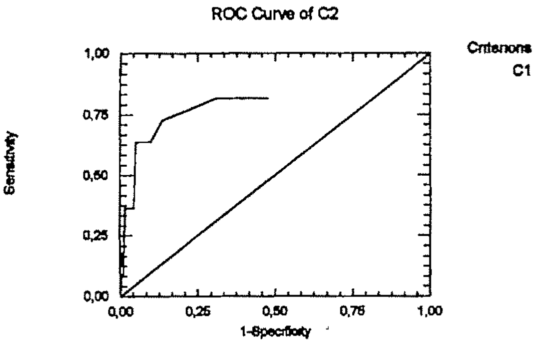
Introduction: Complications of major vascular surgery include unexpected cardiac events which may be predicted by increased Troponin Ic (TnIc) This marker has been reported as sensitive and specific

The aim of this study was to determine the cutoff value of TnIc which may predict cardiac events after aortic surgery.

Methods: 305 consecutive patients undergoing infrarenal aortic surgery were included in a prospective manner Cardiac complications were defined as follows cardiac failure, pulmonary edema, or cardiac death, new Q wave or ST-T depression longer than 48 hours on daily EKG, new akinesia on echography TnIc was dosed within the 1st, 2nd and 3rd postoperative days, using an immunoenzymofluorometric assay on a Stratus autoanalyser (Dade). For evaluation of the ideal discrimination value of TnIc, between the complicated and uncomplicated patients groups, we calculated receiver-operator characteristics for the mean values of the peak of TnIc in the postoperative period.

Results: are reported in the figure

10 patients (3%) developed postoperative cardiac complications 258 patients had TnIc below 0 5 ng/ml, 20 between 0.5 and 1 5 ng/ml and the 27 remaining patients had TnIc higher 1 5 ng/ml



Area under curve is 0 8 (Sd = 0.28) A limit value at 0.6 ng/ml yields to a sensitivity of 73% and a specificity of 86%. A limit value at 1 7 ng/ml yields a sensitivity of 64% and a specificity of 94%

Discussion: A limit value of 0 6 ng/ml is poorly related to cardiac events whereas TnIc level greater than 1.7 ng/ml appears to be correlated with unexpected cardiac events.

A.16 Incidence and causes of cardiac arrests related to anaesthesia in 10 769 administrations

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Background & Goal of Study: Mortality associated with anesthesia has been extensively studied in several countries. (1, 2)

From the results of these surveys, many anesthesia safety standards have been introducted in Europe It sounds interesting to revalue the incidence and the present time causes of anesthetic cardiac arrests

Materials & Methods: For each of the 101769 anesthesias performed at the University Hospital from 1989 to 1995, were gathered patient identification, ASA physical status, anesthetic technique, possible complications Each time a death was not likely related to the surgery, the medical recorded was refered to. The classification in cardiac arrest totally or partially attributable to anesthesia used the INSERM survey definition. (1) Morever, the classification of cardiac arrests were allocated in preventable or not preventable according to The ASA Closed Claims Study. (3)

Discussion & Results: Among 101769 anesthesias, 11 cardiac arrests related to anesthesia were observed· 7 partially and 4 totally attributable to anesthesia. The cardiac arrest incidence was 1.08 per 10000 anesthesias and the incidence of anesthesia mortality was 0 5 per 10000 anesthesias

The main causes of cardiac arrests related to anesthesia was absolute or relative anesthetic overdose ± associated to hypovolemia (1 case in general anesthesia, 3 cases in spinal anesthesia, 3 deaths), Hypoxemia (2 cases in general anesthesia, 1 death), Hypovolemia isolated (2 cases in general anesthesia, no death), Polyfactorial sudden cardiac arrest (2 cases in spinal anesthesia, 2 deaths), 1 case of Pace Maker dysfonctionment (no death).

No cardiac arrests were noted in recovery room, neither during nerve blocks (n = 9227) Ten of 11 anesthetic cardiac arrests were preventable (Table 1)

Table 1 Cardiac arrests preventale nature of human error

Nature of human error	Number of incidence
Inadequate preoperative assessment	6
Anesthetic overdose	5
Inappropriate monitoring	3
Inadequate fluid replacement	3
Inadequate anesthesia technique	2
Hypothermia	1

The main causes of anesthetic cardiac arrest remain identical to the previous surveys There are no anesthetic cardiac arrest in the post operative period as, all the patients were observed in the recovery room

Conclusion: The human error within the genesis of anesthetic accident seem to be essential It's on this point, that the future efforts should deal to improve the safety in anesthesia

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A.17 Morbidity-mortality rates and risk factors after carotid endarterectomy

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Background and Goal of Study: Carotid endarterectomy (CE) is a prophylactic operation designed to reduce the risk of subsequent stroke and stroke related deaths. As such, the effectiveness of profilaxis is directly related to the perioperative risk operation (1) The purpose of this study is to analize the morbidity and mortality rate after CE and their relationship with the preoperative risk factors

Materials and Methods: 103 patients underwent CE with general anesthesia between January 1991 and February 1997 were retrospectively reviewed. Date were analyzed with logistic regression analysis

Results and Discussion: Patients presented the following risk factors. smoking 61%, hypertension (HT) 57%, peripheral vascular disease 38%, hyperlipidemia 30%, coronary artery disease 33%, diabetes mellitus 25%, arrhythmias 15%, chronic obstructive pulmonare disease 7%, chronic kidney failure 5% and congestive heart failure 4% The mortality rate within 30 days of carotid surgery was 1.9% and severe stroke was 0 9% Postoperative complications were recordered in 50% of patients: HT 30%, hypotension 10 7%, bradicardia 9 7%, cranial nerve injuries (hypogloso, facial or recurrent) 9.7%, transient neurologic syntoms 4 9%, angor 4 9%, respiratory insufficiency 4.9%, arrhythmias 3 9%, convulsions 1.9%, myocardial infarctation 2 9% and severe stroke 0 9% The multivariate analyses showed HT as the only preoperative risk factor related with global postoperative complications and coronary artery disease with the development of postoperative isquemic events.

Conclusions: 1.- HT is the only preoperative risk factor related to postoperative complications following CE. 2.- Preoperative coronary artery disease is related with postoperative isquemics events, the most frequent severe complication after CE. 3 - Despite a relative high postoperative morbidity, the rate of combined mortality and severe stroke morbidity is lower than 3% in our centre, being therefore a beneficial and safe surgery for present-day indications

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A.18 Impact of the introduction of a daytime emergency operating theatre in a neurosurgical centre: prospective audit

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Background and Goal of Study: The National Confidential Enquiry into Perioperative Deaths (CEPOD) is an independent audit undertaken in the NHS which aims to identify potentially remediable factors in anaesthetic and surgical practice. The most recent report[1] recommended a reduction in non-urgent surgery performed out of hours by unsupervised trainees primarily through the introduction of 24 hour emergency operating rooms As we were about to introduce a new daytime emergency operating theatre, we decided to audit our out of hours practice both before and following its introduction

Materials and Methods: A prospective audit of all surgery performed between 1800 and 0800 was undertaken for one month before and one month after the introduction of a day time emergency operating theatre The following data was collected for all cases time of arrival at and departure from theatre suite, patient age and sex, ASA status, operation performed, CEPOD category, seniority of anaesthetist and surgeon involved, and whether surgery could have been safely delayed until day time (non-urgent). Data was analysed using Fisher's Exact test and a value of p < 0 05 accepted as significant

Results and Discussion: There were no differences in patient demographics, ASA status or CEPOD category between the two groups. 13 of the 23 operations performed at night during the first month and 3 out of 19 in the second month were non-urgent (p = 0 01) The most senior anaesthetist present was a trainee for 21/23 cases and 9/19 cases (p < 0 01) and the most senior surgeon was a trainee for 19/23 and 10/23 for the first and second months respectively (p < 0.05)

Conclusions: Following the introduction of a daytime emergency operating theatre there was a significant reduction in the number of non-urgent operations performed at night and a corresponding increase in the seniority of both anaesthetic and surgical staff performing out of hours procedures

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A.19 Analysis of documentation of patient data in anaesthetic records in a university teaching hospital

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Background: Anaesthetic Charts are our main record of patient care. Following recent NCEPOD reports (1) and with increasing medical litigation, it is important to audit hospital anaesthetic records.

Aim: To study the quality of information recorded in our hospital's anaesthetic charts and instigate improvements

Method: 124 randomly selected written standard anaesthetic charts (excluding cardiac and obstetrics) from a pool of 66 anaesthetists over a 3 month period, were examined within two days of anaesthesia. Data as suggested by national guidelines (2) were used to assess documentation.

Results and Discussion: The results are shown as a percentage of 124 charts 77% of charts assessed were legible, 23% needed clarification. *Preoperative data.* Patient identification by name, date of birth and hospital number were noted in 97% 96% of patients were seen preoperatively. Only 84% of charts had past anaesthetic details, and if previously anaesthetised in current hospital only 66% of old charts were filed Medical history was noted in 86%, with 43% noting ASA status The fasting status was recorded in 31% Details of airway assessment (56%) and dental state (65%) were poor. A mere 3% recorded height and 14% weight despite their importance. (1) *Intraoperative details:* Only 2 patients out of 3 difficult intubations were Hazard Flagged. 10% charted time of anaesthetic/surgery No charts noted where the patient was anaesthetised or equipment checks 18% noted blood loss. 25% of intubations had grade of larynx noted. 4 records had no vital signs

Conclusion: Anaesthetic records are legal documents They avoid duplication of errors, reflect quality and standard of care. Our study shows deficits in anaesthetic documentation, resulting in incomplete and difficult data retrieval. Poor documentation is difficult to defend legally. Immediate improvement is needed to maintain standards. We suggest emphasis on record-keeping during training, updating and redesigning charts, incorporating national guidelines (2)/checklists. Hazard Flagging in at-risk patients needs standardisation. External assessors from national anaesthetic associations could enforce record keeping to national/legal standards.

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A.20 Perioperative infusion of dobutamine: effects of morbidity and mortality

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Background and Goal of Study: Shomaker's study showed a decrease mortality in high risk surgical patients, treated to rich sovranormal values of cardiac index (CI), oxygen avalaibility (DO2I) and oxygen consumption (VO2) [1]. Aim of this study was to see if perioperative infusion of dobutamine, following as therapeutic goal an extimated oxygen extractio (O2ER) lower then 26.7% (the optimal value found by Shoemaker for oxgen extractio [1]) can reduce mortality and/or morbidity in a group of high risk surgical patients

Material and Methods: We have performed a multicentric, prospective, randomized study on high risk surgical patients The protocol study was approved by the Ethic Commitee of Ancona University, Italy. Admission criteria were the same then Shomaker's ones and a written consensus was asked After the admission the patients were radomized in the control or in the protocol group. Before the operation a central vein and a catheter in radial artery were positioned. Controls of emogasanalisis, central venous pressure, arterial pressure, O2ER were made preoperatively, during operation every hour, half an hour after operation, 1, 2, 4, 6, 18 hours after the end of the operation. O2ER was calculated with the following formula. SaO2-SvO2/SaO2. In the control group the therapeutic goal was to achieve normal value of blood arterial pressure and diuresis, while in the protocol group the therapeutic goal was mantain an O2ER < 26 7% In the protocol group if an O2ER higher then 26.7% was found, the following therapeutic steps were made· liquid infusion (blood if Hb < 10 g/dl), then dobutamine infusion (5–15 γ/Kg/min.). At the hospital dicharge a dimmission paper for each patient were organ failures were signed Chi-squared test was performed to show any significative difference in morbidity and mortality

Results: 165 patients were admitted, but of these we have the final data of 135 patients 68 were in the protocol group and 67 in the control group There was no difference in mortality (2 death both in protocol and control group), while a significative difference were shown in number of patients with organ failures (8 in protocol group vs. 20, p < 0.05), total number of organ failures (9 in protocol group vs. 27 in control group, p < 0.01)

Conclusions: These data suggest that maintaining an O2ER higher then 26.7% perioperatively can reduce morbidity in high risk surgical patients

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A.21 Effect of thoracic epidural analgesia on postoperative complications after cardiac surgery – a prospective study

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Objective: To assess prospectively the effects of thoracic epidural analgesia on postoperative complications in cardiac surgical patients and the incidence of complications arising from this use of this technique

Method: After gaining informed consent 120 patients were prospectively randomised to receive either thoracic epidural analgesia (TEA) using bupivacaine and clonidine or target controlled infusion (TCI) of alfentanil for analgesia during and after elective coronary artery bypass graft surgery. Anaesthesia was standardised using TCI propofol. Data were collected for the first 5 days and included demographic data, the incidence of complications & time taken to extubation. Results were analysed using χ_2-test on Minitab. Inspiratory volume was measured preoperatively and at 24 hrs postoperatively and the results were compared using the Mann-Whitney U test

Results: No significant differences between the two groups were found with respect to age, sex, ejection fraction, no. of grafts performed, incidence of preoperative respiratory disease, hypertension or diabetes. Bypass and ischaemia times were similar between the two groups Patients undergoing thoracic epidural analgesia were extubated sooner than those using TCI alfentanil (p = 0.05) with a lower incidence of respiratory tract infection (p = 0.048). There were no significant differences between the two groups with respect to other complications or the use of inotropes although this approached significance (p = 0 06) There was a trend for the inspiratory volume to be reduced more in the TCI group although this did not reach statistical significance. 14 patients in the TCI group and 9 in the TEA group were still intubated at 24 hrs and were excluded from this part of the anaylsis There were no serious neurological or other complications arising from the use of TEA in this series of patients.

Conclusion: TEA provides excellent analgesia for the cardiac surgical patient and allows early extubation with decreased incidence of respiratory tract infection in the postoperative period There is also a trend towards decreases in other postoperative complications such as arrhythmias and use of inotropic agents in patients who receive TEA

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A.22 Influence of cardiopulmonary bypass-related factors in postoperative renal failure

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Background and Goal of Study: Acute renal failure (ARF) is a serious complication after cardiopulmonary bypass (CPB). Several intraoperative factors are related with the developement of ARF type of flow, hemolysis, hypothermia, duration of CPB, microemboli from CPB, drugs used, hemodinamyc changes etc. The goal of this study is to assess the influence of CPB-related factors in the developement of postoperative ARF

Material and Methods: We evaluate 200 patients undergoing cardiac surgery with total CPB and normal renal function was assessed before the operation. *General patient management.* standard general anesthesia for cardiac surgery was used. CPB was managed with nonpulsatil perfusion Systemic flow was targeted at 2–2.5 l/m/m^2 or 1 6–1 8 l/m/m^2 (normothermia/hypothermia) to mantain a mean arterial pressure of 70 mmHg and 30–70 mmHg respectively. Mannitol was routinely administered *Data collection.* A) CPB information (systemic flow, MAP during CPB, duration of CPB, time of aortic cross-clamping) B) Intraoperative complications C) Hemodynamic values, including pulmonary artery pressures and cardiac output *Statistical analysis·* chi-square, Student's t and logistic regression analysis. *Patient classification:* Class I: patients with ARF (serum creatinine >2 mg/dl); Class II: patients with normal renal function

Results and Discussion: 26 patients developed ARF (13%) Comparing duration of CPB in Class I patients (144.5 ± 84 5 min) with Class II patients (101 2 ± 39 6 min), we observed a statistically significant difference (p < 0 05). Other CPB-related factors did not correlate with the developement of ARF However, the variable "duration of CPB" implies the existence of several surgical and hemodinamyc factors that could be related with postoperative ARF independently of CPB-related factors *per se.*

Parameters of CPB and postoperative renal failure

	Class I	Class II
CPB flow (L/min)	1.98 ± 0.38	2 11 ± 0 38
Duration (min)	144 5 ± 84 5*	101 2 ± 39 6
MAP (mmHg)	64 ± 13 6	71 8 ± 16 5
Ao cross-clamp (min)	83 2 ± 40 9	74 ± 33 2

Conclusion: Among CPB-related factors only the duration of bypass seems to be related with postoperative renal failure This particular factor also involves variables not related to CPB.

A.23 Fast-track recovery in cardiac surgery: experience in a public hospital

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Background & Goal of Study: Fast-Track (FT) recovery is a method to reduce hospital stay (less than 5 days, <5 d) for pacients undergoing cardiac surgery (CS) Based on economical purposes it was started in USA in the 90's. The aims are faster extubation and earlier discharge without increasing morbility or mortality.

Material & Methods: All patients undergoing CS from February to July 1995 with no exclusion criteria (age >70 yr, FVC, FEV1 < 50%, creatinin >147 mmol/l, FEV₁ < 30%, NYHA ≥ 3, patient or family rejection; non elective surgery Preoperative: patient and family information. Anaesthesia: fentanyl <15 μg/Kg with isoflurane or propo. Aprotinin to reduce blood loss and steroids Postoperative early extubation and ambulation. Discharge on specific protocol· stable rythm, Hb > 80 g/l, T < 37.8°C, no ambulation problems, acceptance by patient and family.

Results & Discussion: 229 patients with CPB, 44.5% (102) included in FT No patient rejected to be included. 58 8% (60) were discharged ≥5 d (group A). 41.2% (42) were no suitable (discharge >5 d, group B), 3 9% (4) deaths Preoperatively patients from group A presented less incidence of DM, previous vascular surgery and renal disfunction than group B. There were no significant differences in type of surgery, CPB and aortic clamp times Post-operative complications· 3.4% in group A and 52 7% in group B (p < 0 0005) Statistically significant differences (p < 0 05) were found (A vs B, %) pulmonary (1.6 vs 29), ARF (0 vs 26 3), reoperation (0 vs 13) Also FT statistically significant results (p < 0 005) were (A vs B) extubation time (hours). 6 vs 9, PO-ICU (days) 1 8 vs 3.8, Discharge (days) 4 8 vs 7.7. Causes of discharge delay (%) were inadecuated anticoagulation (26.3), pulmonary (23.7), disrhythmias (18 4), fever (10 5), and neurologic disorders (5 2)

Conclusions: 60% of candidates to FT were discharged before 5 days without any increase in morbility/mortality. Preoperative renal disfunctions and postoperative pulmonary, renal or bleeding complications were discriminatives to delay extubation and discharge Length of stay reduction led to admission of new patients Thus, hospital expenses were increased. FT do not add any savings in our public health system.

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A.24 Serum creatinine cannot predict renal impairment in the perioperative period

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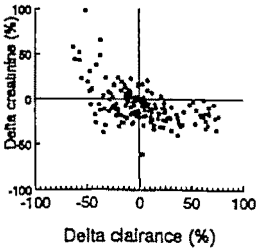
Background and Goal of Study: Serum creatinine increase is routinely used to detect postoperative renal dysfunction although this parameter is considered by nephrologists to have a poor sensitivity in the detection of renal dysfunction

Material and Methods: We used the 2 h-creatinine-clearance (CC) as a reference method (1). The major issue in the CC determination was the necessity of collecting urine accurately For this reason, patients with anticipated difficulties to perform CC were excluded psychiatric illnesses, prostatic problems. 3 hours before CC measurement, patients were asked to drink half a litter, to obtain a regular output CC measurements were performed between 12 h and 17 h to minimise diurnal variations All the procedure was checked by a physician 182 patients scheduled for aortic surgery, without CPB, (120 aneurysms, 62 stenosis) were analysed, mean age 66 ± 10 years (Males n = 164) Serum creatinine and CC were measured in the preoperative period and at day 7 Renal impairment was defined as a 20% increase in serum creatinine or a 20% decrease in CC

Results and Discussion: Considering CC, 28 patients (15%) had a renal impairment in the postoperative period, as compared to 13 patients (7%) considering serum creatinine Serum creatinine sensitivity was 0 46 (CI 95%. 0 37–0 55); its specificity was 0 99 (CI 95%: 0 98–1 00). Figure I shows the poor correlation between serum creatinine and CC modifications, Spearman test R = 0 50.



Conclusion: Serum creatinine increase has a low sensitivity in renal impairment diagnosis in the perioperative period. The use of CC is therefore mandatory in clinical studies assessing risk factors for renal dysfunction

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A.25 Patient knowledge of anaesthesia and perioperative care in an Irish teaching hospital

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Background and Goal of Study: Recently the public has taken an increasing interest in medicine. However, its perception of anaesthetic care and the role of anaesthetists appears to remain limited (1, 2) Inadequate understanding of medical terms may limit the validity of informed consent and compromise the value of the preoperative visit We examined patient knowledge and attitudes concerning perioperative care and the role of the anaesthetist and determined what, if any, improvement in patient knowledge occurred during an elective inpatient stay

Materials and Methods: Following ethical approval, 300 patients answered a multiple choice questionnaire asking them meanings of commonly used medical terms, knowledge of anaesthesia and expectations and fears concerning surgery, pain and anaesthetic care. Patient groups were surveyed either before their preoperative visit, after the visit, or after surgery.

Results and Discussion: Knowledge of commonly used terms including fasting, drips, catheters, nasogastric tubes, and their functions was limited 25% of patients believed that oxygen was an analgesic or antiemetic These deficits were not improved by preoperative visiting or postoperative ward exposure Patients' understanding of the role of the anaesthetist in their perioperative care was similarly limited, although this improved during hospital stay. Only 49% of patients surveyed prior to preoperative assessment knew that anaesthetists were medically qualified This increased to 72% after the visit but declined to 64% postoperatively, with similar findings for anaesthetists' role in intraoperative and recovery care, demonstrating the transience of the knowledge acquired. Comparable proportions of patients admitted to fear of surgery, postoperative pain, awareness, and death Females and young patients feared awareness most In general, female, younger, higher SE group patients had greater knowledge and expectations

Conclusions: Patient knowledge concerning perioperative care remains limited and improves only marginally during hospital stay If increased patient participation is to be realised it will require novel approaches to patient education.

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A.26 Unintended decreasing body temperature: a stepchild of perioperative care and outcome consequences

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Background & Goal of Study: Recent sudies indicate an association between hypothermia, increased blood loss, increased morbidity rates, longer hospitalization and increased mortality rates (1, 2). The purpose of this study was to prospectively evaluate whether perioperative decreasing body temperature is a problem in our surgical patients and whether it influences postoperative outcome.

Material & Methods: On admission at our ICU the rectal body temperature of 207 surgical patients was used to form four groups. All patients were scored by POSSUM. The POSSUM score defines the severity of illness following admission to the ICU and allows a more precise prognosis for the patients population to be assessed before treatment commences. Complications, the length of stay and the survival/death on the ICU were documented.

Results & Discussion: Perioperative hypothermia of patients during major surgery is frequently observed in our hospital. Only 23.6% of our patients were admitted with core temperatures over 36.0°C. The groups did not differ with regard to the POSSUM-predicted morbidity or mortality. In contrast we observed elevated incidences for morbidity and mortality from mild hypothermia to severe hypothermia. These differences were significant for mortality (p = 0.0031/Chi-squared analysis with Fisher's exact test). In addition hypothermia was an independent predictor for mortality by multivariate analysis of variance (p = 0.0087).

Group	(%)	Temp. (°C)
1 (n = 049)	23.6 Normothermia	>36.0
2 (n = 116)	56.0 Mild unindended hypothermia	35.9 – 34.0
3 (n = 038)	18.3 Moderate unintended hypothermia	33.9 – 33.0
4 (n = 004)	1.9 Severe unintended hypothermia	<33.0

Group	Lenghth of stay (days) mean/Range	Complication-rate (%) predicted/observed	Mortality (%) predicted/observed
1	4.51/2–30	20.0/24.0	6.0/8.2
2	4.15/1–29	18.0/18.0	4.9/0.9
3	5.97/2–37	21.7/18.0	7.7/16.0
4	3.75/2–9	29.6/25.0	9.4/25.0

Verification of the isolated influence of unintended hypothermia is only possible if the preoperative risk and surgical management is comparable in both, the normo- and hypothermia group. Comparing groups with the same score-predicted risk, this is the first prospective study showing that unintended hypothermia results in an increased postoperative mortality, and that hypothermia is an independent predictor for postoperative mortality.

Conclusion: Our data suggest that maintaining patients normothermia means to improve patients outcome.

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A.27 Single-dose antiemetic treatment of postoperative nausea and vomiting in the recovery room is insufficient

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Background: Postoperative nausea and vomiting (PONV) is a frequent problem in the recovery room and on the surgical ward [1]. This prospective, epidemiological study determined the relationship between early occurrence of PONV in the recovery room on the patient's outcome on the ward.

Methods: During a 4-month period 1000 patients undergoing a wide variety of surgical procedures were observed in the recovery room for the occurrence of nausea and vomiting and then followed up postoperatively for a period of further 24 hours.

Results: The total incidence of PONV was 36.4%. 165 patients (16.5%) suffered from PONV in the recovery room. 128 of them (77.6%) were treated with antiemetics (metoclopramide, dimenhydrinate, droperidol, and tropisetron). After complete relief of PONV, patients were transferred to the ward (median times in the recovery room: patients with PONV: 100 min; patients without PONV: 75 min). There however, 331 suffered from PONV. Patients who have previously shown symptoms in the recovery room had more than a 4fold increased risk for PONV later on the ward (see table). Furthermore these patients suffered from more severe PONV than patients who developed PONV only later on the ward.

There was a trend towards a lower rate of reappearance of PONV in patients who were trated with longer acting antiemetic drugs (droperidol, tropisetron) or received a prophylactic antiemetic treatment with repeated doses of shorter acting drugs (metoclopramide, dimenhydrinate).

Recovery room	Surgical ward
Without PONV (n = 835):	remained syptom-free: 76.2%
	developed new PONV: 23.8%
With PONV (n = 165):	were cured from PONV: 20.0%
	had persistent PONY: 80.0%

Conclusion: Patients suffering from PONV in the recovery room have a very high risk for persistant severe PONV on the surgical ward, even when their antiemetic treatment in the recovery room has been successful.

Thus, in these patients, longer acting antiemetics should be prefered to treat PONV in the recovery room. Otherwise, when short acting antiemetics are used, their administration should be repeated to ensure effective plasma levels of the drug.

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A.28 Multifactorial treatment including ondansetron eliminates postoperative nausea and vomiting

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Background and Goal of Study: Nausea and vomiting is a "big little problem" after gynaecological surgery [1]. This study compares the effectiveness of metoclopramide and dexamethasone vs metoclopramide, ondansetron and dexamethasone in the prevention and treatment of PONV in patients premeditated i.v. with droperidol scheduled for total abdominal hysterectomy (TAH).

Materials and Methods: 410 patients ASA 1 and 2 received at the induction of general anaesthesia 1 mg droperidol i.v., then. fentanyl, thiopentone and suxamethonium following 3 min oxygenation. Anaesthesia was maintained with 66% nitrous oxide in oxygen, halothane up to 0.5 vol% and atracurium; on pain stimuli fentanyl was added. IPPV ventilation supplied patients with 10 ml/kg of tidal volume via endotracheal tube. At the end of surgery the patients were blindly randomized to be administered i.v. either metoclopramide 10 mg plus dexamethasone 8 mg or the same doses of metoclopramide and dexamethasone and 4 mg ondansetron. All the incidents of PONV were recorded by the nursing staff hourly for 12 hrs. Data were analyzed using chi-square test; p < 0.01 was considered statistically significant.

Results: Age, weight, height and duration of anaesthesia were similar between the groups. Postoperatively none of the 205 patients of the ondansetron group showed any evidence of vomiting.

	Group without ondansetron	Group with ondansetron
Number of patients	205	205
No PONV	127 (62%)	200 (97.6%)
Nausea >10 min	12 (5%)	2 (0.9%)
Vomiting	21 (10%)	0 (0%)

It appears that the synergistic, multifactorial therapy of PONV enhanced with ondansetron can be highly effective in N2O and fentanyl supplemented anaesthesia for major gynaecological surgery (p < 0.001) [2].

Conclusion: Ondansetron in a single i.v. dose of 4 mg in combination with droperidol, metoclopramide and dexamethasone actually eliminates PONV.

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A.29 Sixty per cent of patients can be extubated in the operating room after orthotopic liver transplantation

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Background & Goal of Study: Improvements in surgical technique of orthotopic liver transplantation (OLT) and experience with severely ill patients led us to explore the possibility and safety of extubating OLT recipients in the operating room (OR)

Material & Methods: From 01/1995 to 09/1997, 248 OLTs were consecutively performed in 227 patients The piggy-back technique without veno-venous by-pass was routine (>95% of the cases) OR extubation was performed within 90 minutes after the end of surgery Its feasibility was jointly evaluated by the anesthesiologist and the surgeon, according to these criteria haemodynamic stability without active bleeding nor amine use, adequate graft function (improvement of coagulation tests and base deficit), absence of encephalopathy, no use of antagonist drugs except for neuromuscular reversal Data are expressed as mean ± SEM

Results: 149 OR extubations were performed in the 248 OLTs (60%) The rate of OR extubation increased with time (1995 49%, 1996 61%, 1997: 74%). Preoperative features of OR extubated patients were a) age. 48 ± 1 years (range 16–67), with 73 patients aged more than 50, b) UNOS status· I (patient at home, active), 18 patients (12%), II (at home, with frequent hospital interactions), 106 patients (71%); III (continuous hospitalization in acute care bed), 25 patients (17%), IV (life expectancy <7 days), no patient Intraoperative features were a) surgical time 351 ± 7 minutes (range 165–545), b) total blood requirement 8 5 ± 0 5 PRBC units (range 0–32), with 39 patients receiving >10 units, c) final PaO_2/FiO_2 ratio· 442 ± 9 (range 161–705); d) final body temperature always >36°C The time to OR extubation averaged 29 ± 2 minutes Forty-five OR extubated patients (30%) were discharged directly to a surgical middle care unit Only one patient was reintubated within 24 hours because of oversedation and hypercapnia

Conclusions: OR extubation after OLT is feasible and safe in 60% of the patients Contrarily to what previously suggested[1], age >50 years, UNOS III status and total blood requirement >10 PRBC units do not preclude OR extubation This practice is an effective alternative to prolonged postoperative sedation and can reduce the need of intensive care hospitalization in OLT recipients

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A.30 Preoperative risk factors for postoperative renal impairment after aortic surgery

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Background and Goal of Study: The development of postoperative renal failure is a serious complication occurring in 1–50% patients, depending on the population studied (1). The aim of the study was to prospectively assess preoperative risk factors for a postoperative renal impairment

Material and Methods: We defined a renal impairment as a 20% decrease in creatinine clearance (CC) between the preoperative and the postoperative (day 7) period. 245 scheduled patients for aortic surgery were enrolled in the study over a 2 year-period Non scheduled patients, planed CPB, chronic extrarenal epuration were excluded. The following preoperative variables were considered. sex, age, coronary disease, hypertension, left ventricular ejection fraction, radiocontrast agents administration, angiotensine converting enzyme inhibitors (ACEI) use, diuretics use, respiratory insufficiency, renal disease, diabetes mellitus, hyperuricemia, cerebral vascular disease, cancer, preoperative serum albumin, haemoglobin and calcium concentrations and peroperative variables· surgery duration, sepsis, peroperative hypotension, aprotinine administration, transfusion, colloid and crystalloid loading A forward stepwise logistic regression (criteria for entry, $P < 0\ 05$) was used, odds ratio and 95% confidence interval (CI) were calculated

Results: Extrarenal epuration was required in 3 patients in the postoperative period. Postoperative renal dysfunction occurred in 59 (24%) patients. Only preoperative ACEI use (odds ratio· 1.93, 95% CI 1–3 77) was significantly associated with postoperative renal impairment

Conclusion: We therefore concluded that postoperative renal impairment, defined as a 20%-decrease in CC, was significantly related to one preoperative predicted factor ACEI use.

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A.31 Anaesthetic morbidity during laparoscopic surgery

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Laparoscopic surgery is extensively used and is reported to be safe. However insufflation of the abdomen by CO_2 significantly impairs respiratory and cardiovascular function and may have deleterious side-effect We therefore conducted a multicentre epidemiologic survey to assess anaesthetic morbidity related to laparoscopic surgery

Patients and Methods: The study was prospectively conducted over one year in 25 surgical centres All the patients scheduled for laparoscopic surgery during this period were included Data were collected from a predetermined questionnaire which focused on patients features, type of surgery, monitoring, and complications They include ventilatory (e g pneumothorax) cardiovascular (e g severe hypotension or cardiac arrythmia) and surgical (e.g haemorrhage) complications An univariate analysis and then a step by step logistic regression were used to determine the risk factors of complications

Results: 2610 patients were included in the study and 493 (18.9%) suffered from at least one complication. Among the 582 complications, 54% were surgical ones, 23 7% were respiratory and 18 7% were hemodynamic ones Univariate analysis pointed out 17 factors significantly associated with complications, 7 of these persisted as independent risk factors (RF) in the multivariate analysis (table).

RF	OR	95% CI	P
Type of surgery	2 39	1 53–3 74	<0 00001
centre	6 77	3 86–3 74	<0 00001
ASA	1 78	1 35–2 35	<0 00001
Chronic respiratory failure	2 46	1 38–4 39	<0 00001
Weight	1 82	1 21–2 74	<0 0021
Sex (w)	0 7	0 56–1 01	<0 04
Insufflation pressure	1 45	1 04–2 02	<0 06

According to our model, we were able to adequately classify 66% of the patients in complicated or uneventful surgery Using the first 4 risk factors of this model allowed to predict an adjusted risk varying between 1 44 and 70 8

This study documents that close to 1 over 5 patients scheduled for laparoscopic surgery experience at least one adverse event The rate of complication is highly influenced by the type of surgery but it is also independently related to the surgical centre. This risk can be predicted according to patient physical status

A.32 Early morbidity and mortality and risk factors in patients undergoing lung resection for lung carcinoma

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Background and Goal of Study: Morbidity and mortality rates for pulmonary resections remain significant Morbidity ranges from 7 to 50 percent, and mortality from 2 to 12 percent, despite advances in anaesthesia, surgical techniques and perioperative care. Cardiac and pulmonary complications are the major sources (1, 2)

The aim of the study was to evaluate the early morbidity and mortality rates in patients undergoing major pulmonary resection for lung carcinoma, and to identify risk factors

Materials and Methods: One hundred and ninety nine patients underwent pulmonary resection (lobectomy and pneumonectomy) for lung cancer between December 1994 and September 1997 were retrospectively reviewed The following were recorded Age, sex, ischemic cardiopathy as a risk factor, tumoral stage, surgical procedure, preoperative evaluation of respiratory function and perioperative complications (only if a medical intervention was required).

Mortality risk asociated with selected factors was evaluated using multiple logistic regression analysis

Results and Discussion: 199 patients, 186 males and 13 females, were studied (70 pneumonectomies and 129 lobectomies) The median age of patients was 63 years (range 35–6) ASA score II–III. Twenty four patients (12%) presented previous ischemic cardiopathy Perioperative complications were absent in 143 patients (72%) Forty three patients (22%) had postoperative pulmonary complications and 21 patients (10%) cardiac complications There were seventeen postoperative deaths (8 5%) Patients with a preoperative FEV1 less than 50% of predicted had a mortality rate of 33% and complications occurrence in 66% There were no intraoperative deaths. In a multivariate analysis, none studied factor seems to be predictive about occurrence of death FEV1/FVC appears to be the best high risk indicator.

Conclusion: Our results suggest that preoperative risk factors such as ischemic cardiopathy and pulmonary function should not deny the pulmonary resection Occurrence of perioperative complications is associated with an increased risk of death Pulmonary complications continue to be the major source of morbidity.

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A.33 Rate of lower respiratory tract infection in intensive care units: an Italian multicentre observational study

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Introduction: The current problems/controversies on epidemiology and management of hospital-acquired infections are of particular concern for patients admitted to intensive care unit, for which severity of illness, length of hospital stay, invasive diagnostic procedure and appropriate treatment could represent, among other, risk factors in the development of severe respiratory complication.

An Italian Observational Study in Intensive Care Unit and relative Microbiological Department has been planned to mainly investigate in ventilated ICU patients:

(a) Rate & Characterisation of bacterial infection at low respiratory level
(b) Pattern of antibiotic susceptibility

Preliminary general data are here presented.

Methods: 36 ICU Centres in collaboration with their respective Microbiological Dpt. participated to the study. According to common protocol criteria and a 3 months study period, consecutive admitted ICU ventilated-patients have to be observed for 7 days. A 1st microbiological sampling was obtained on admission to the ICU by means of a protected bronchial catheter (Combicath®); a 2nd sampling was similarly performed in still ventilated Pts. at 7th day or prior in those subjects which developed pneumonia. All samples were evaluated for pathogen identification, CFU value and antibiotic testing. Data on admission diagnosis, former antimicrobial therapy and in-out patient provenance were also collected.

Results: Up to now 557 cases are included in the study. 367 of them (66%) were in-patient, previously hospitalized in surgery (42%) or in other Clinical Dpt: almost 1/3 came from emergency room. On ICU admission 60% of the Pts were already intubated, for an average length period of 6.4 hours. At 1st sampling, colonizations (24.2%) or infection (13%) occurrence were respectively observed. Among longitudinally evaluated pts, 57 (10.2%) developed a LRT complication, nearly 38% of them within day 2 following ICU admission. *S aureus* (20), *Pseudomonas aer.* (11), *Acinetobacter spp* (4), *Haemophilus spp* (3), *neg coag S* (3) were the most frequently observed pathogens.

OUTPATIENT ANAESTHESIA

A.34 Inhalational induction for day-case anaesthesia: patient and anaesthetists' acceptability

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Background and Goals of Study: Sevoflurane offers the opportunity for potentially beneficial inhalational induction (IHI) in daycase surgery[1], despite this its use appears limited. The aim of this study was to determine views of anaesthetists and patients on IHI and to compare its use with our current standard technique for daycase anaesthesia.

Materials and Methods: Questionnaire surveys of daycase pts. *(n = 150)* & anaesthetists *(n = 95)* were carried out together with a prospective randomised open two group study of pts. undergoing daycase gynaecological surgery *(n = 24). Group 1:* Sevoflurane induction/maintainence. *Group 2:* propofol induction/sevoflurane maintainence Patient acceptabilty, morbidity & recovery characteristics were studied. Results were compared using a chi squared test

Results and Discussion: 47% of pts. preferred IV induction (IVI), 44% had no preference & 9% preferred IHI. Of pts. who had had previous GA (77% of total), 98% found IVI acceptable, compared with only 43% for IHI.

Of anaesthetists surveyed, none used IHI as the method of choice in adult pts, the primary indication for IHI being airway difficulties (98%), 71% considered pt. choice an indication. The most commonly believed disadvantage was pt. unacceptability of the technique (83%). Over 80% of anaesthetists would choose to use sevoflurane for IHI. Randomised comparison with IVI showed a much improved pt. accepability of IHI (100% accepability in both groups) and comparable morbidity (see table) & recovery charateristics. PONV and dizziness were increased in IHI, but this was not statistically significant possibly due to the small sample size.

	PONV	Headache	Dizziness	Somnolence
Group 1*	4	4	5	2
Group 2*	1	4	3	2

*$n = 12$

Conclusion: IHI was perceived to be an unpopular choice by pts. and anaesthetists alike. However when compared in the randomised study, IHI with sevoflurane appeared as acceptable to pts. as IVI. Bias against IHI amongst anaesthetists and pts. may continue to restrict the use of this potentially beneficial technique.

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A.35 Propofol *vs* sevoflurane in short surgical gynaecological procedures

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Background and Goal of Study: Propofol induced anesthesia and manteinance is a well studied and safe technique for short gynecological surgery.(1) Experience with Sevoflurane, in U.S.A. and Europe, has shown it as an alternative because it's a safe and rapid drug for induction and manteinance of anesthesia.(2) We have compared both techniques (intravenous and inhalatory) and a combined one with propofol and Sevoflurane.

Material & Methods: We have studied 50 patients scheduled for short gynecological procedures and randomized in 3 groups: Group 1: Propofol induction 2.5 mg/Kg and manteinance at 5–6 mg/kg. Group 2: Propofol 2.5 mg/kg and Sevoflurane 1–2% for manteinance. Group 3: Sevoflurane for induction (vital capacity technique) and manteinance 1–2%. All patients were ventilated with O2/N2O at 40/60 and laringeal mask was applied. All patients received prior to induction Fentanilo at 1–2 μgr/kg. We excluded pregnant patients, morbid obesity, liver or kidney disease, or surgery in previous 7 days and ASA >II. Standard monitorization

Results and Discussion: All groups were homogeneous. We didn't find significative differences in induction times or laringeal mask insertion between groups 1&2 vs 3. We didn't find significative differences neither in induction characteristics nor in haemodinamic stability among three groups. There are significative differences in quality of inmediate awakening between groups 1&2 vs 3 (nausea, vomiting) and 24 hours after surgery ($p < 0.05$). Patients of group 3 had more pain 2 hours after surgery ($p < 0.01$), but we didn't find differences 24 hours pain.

Conclusion: Induction with Sevoflurane is an alternative for the anesthesiologist but we conclude it increases the incidence of nausea and vomiting in patients scheduled for ginecological surgery and the patients feel more pain at the inmediate postoperatory period.

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A.36 A double blind comparison of sevoflurane *vs* propofol and mivacurium for tracheal intubation in day case wisdom tooth extraction

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Background and Goal of Study: Propofol and mivacurium are commonly used in day case anaesthesia but both drugs have adverse effects. Sevoflurane provides a rapid, smooth induction, acceptable to the majority of patients[1] and permits tracheal intubation,[2] but has not been compared with an iv induction-muscle relaxant technique.

Materials and Methods: 24 (ASA I–II) patients undergoing day case wisdom tooth extraction were randomly allocated to receive propofol-mivacurium-isoflurane or sevoflurane. After obtaining written consent an iv cannula was sited and oxygen (5 L min^{-1}) was delivered by facemask. After 1 min, fresh gas flows were changed to oxygen, 2 L min^{-1}, and N_2O, 4 L min^{-1}. The inhalation induction group received 8% sevoflurane with manual ventilation after loss of consciousness until intubation. The iv induction group received propofol 2–3 mg kg^{-1}, isoflurane, 1%, and mivacurium, 0.2 mg kg^{-1}. Nasal intubation was performed at 4 minutes, in both groups, by a blinded anaesthetist and conditions were graded using the Krieg and CCC scores. All patients received ibuprofen and bupivacaine infiltration for analgesia. Time to start of IPPV, completion of intubation and emergence times were recorded. NIBP was measured prior to induction and at 1 minute intervals. Average costs were calculated using UK prices. Data (mean ± SD or median and IQR) were analysed by ANOVA, nonparametric and Fishers exact tests, as appropriate.

Results and Discussion: The two groups were demographically comparable. Intubation was completed at 281 ± 62 s and 293 ± 52 s with propofol-mivacurium and sevoflurane, respectively. Intubation scores and conditions did not differ significantly between the groups (table). MAP was significantly higher in the iv group at 7 (104 ± 15 *versus* 88 ± 16 mmHg) and 8 min (104 ± 18 *versus* 79 ± 13 mmHg) compared to the sevoflurane group. Emergence times were similar (table). Based on actual drug used to complete intubation, the sevoflurane technique cost significantly less at £5.77 *versus* £6.80.

	Propofol-mivacurium	Sevoflurane
Kneg score	3 (3–5)	4.5 (3.5–6.5)
CCC; Clinically. acceptable (n)	11	11
unacceptable (n)	1	1
Eyes open (min)	6.0 ± 2.3	5.1 ± 1.0

Conclusion: This study shows that providing adequate induction times are used, sevoflurane induction provides comparable intubating conditions and is cheaper than a propofol mivacurium technique. However, a larger sample would be required to detect uncommon side effects.

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A.37 Sevoflurane *vs* propofol in day-case surgery anaesthesia

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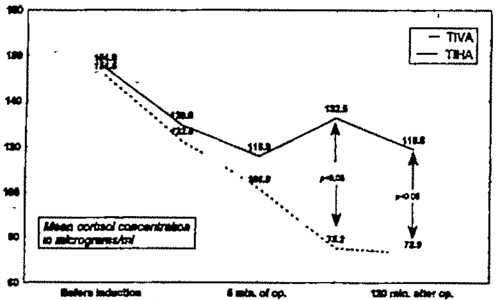
Goal of Study: Comparison of two different method of general anaesthesia in day-case surgery.

Materials & Methods: 60 women; aged 18–60 yrs; ASA I or II. Operation: excision of cystic mammary displasia. Oral premedication: midazolam. Group A – TIVA (induction: propofol 1.5–2.0 mg/kg + alfentanyl 7 μg/kg; maintenance: propofol by Prys-Roberts rule + alfentanil 1 μg/kg/min.); group B – inhalation anaesthesia "TIHA" (induction. sevofluran 7% vol + 50% O_2/N_2O; maintenance: sevofluran 1–2% vol + 35% N_2O/O_2). Patients breathing spontaneously via laryngeal-mask. Ventilation was supported when apnea >15 s. occurred, tachypnoe was >30 and MV decreased more than 30% of baseline. We measured: the number of patients needing ventilation support (Supp. Vent.), awakeing time (Aw. T.), response time (Res. T.), orientation time (Orient. T.), discharge time from recovery room (Disch. T.), home ready time (Home Ready T.), p-deletion test and cortisol concentration. Side effects were reorded. Postop. pain was treated with NSAID-s.

Results: There were no significant differences in p-deletion test and vomiting/nausea. Side effects (TIVA v. TIHA; $p < 0.05$): pain (20% v.70%), dizziness (6% v.60%), sedation-VRS >0 (10% v 0), apnea (6% v.0) and drowsiness (50% v. 14%). Other results are shown in the tabele ($p < 0.05$).

	Group A	Group B	
Supp. Vent	n = 30	n = 21	$p < 0.05$
Aw T. (min.)	5.7 ± 2.64	4.7 ± 1.97	ns
Res T. (min)	6.8 ± 2.85	5.4 ± 1.91	$p < 0.05$
Orient T. (min)	7.9 ± 3.08	6.1 ± 2.09	$p < 0.05$
Disch T. (min)	33.2 ± 6.75	21.7 ± 5.17	$p < 0.05$
Home Ready (min)	137.3 ± 21.73	73.7 ± 13.73	$p < 0.05$



Conclusions: 1. In both groups ventilation support was applied. 2. In TIHA group patients needed pain treatment more frequently and earlier than in TIVA group. 3. TIHA (sevofluran + N_2O/O_2) is safe and comfortable for patients and they could be transferred from recovery room to DCS dep. quicker than after TIVA (propofol + alfentanil).

A.38 Sevoflurane *vs* propofol for ambulatory anaesthesia: a cost-effectiveness analysis

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Background & Goal of the Study: Inhaled induction and maintenance of anaesthesia with sevoflurane (S) in adults is as safe and reliable than with IV propofol (P). This prospective randomised study compares the cost and the adverse events during and after induction and maintenance of ambulatory anaesthesia either with S either with P.

Patients & Methods: Fifty two, ASA I female adult patients scheduled for pregnancy termination by curettage were included after CPPRB approval and written informed consent. After premedication with lorazepam. 1 mg, 2 hours before surgery, anaesthesia was induced with 0.5 to 0.75 mg alfentanil and either P (2–3 mg/kg), (n = 26) either with S (8%, 6 l/min O2) (n = 26) using the single breath vital capacity technique. Anaesthesia was maintained with N_2O in both groups and either 20 mg P boluses either S (2 to 3% in 2 1 fresh gas flow) according to the clinical signs of depth of anaesthesia. Standard cardiovascular and respiratory monitoring data were recorded each 2 min after the start of anaesthesia. The doses and length of administration of gas and anaesthetics were measured to calculate the cost. The delay of induction (loss of eyelash reflex, fixed pupils), the time to respond to verbal command, to say one's name and birth date after the end of administration of N_2O (group P) and S (group S) were measured. Adverse events were prospectively recorded during anaesthesia and in the recovery room. Patients were asked to answer to a detailed questionnaire about their subjective feeling at the exit of the recovery room and at the 24th postoperative hour. A Fisher's exact test or a chi-2 test were used to compare non parametric data. An anova test was performed with parametrical results. Results are expressed as mean ± SEM. $P < 0.05$ was considered significant.

Results: The demographic data, the length of anaesthesia and stay in the recovery room were not statistically different between the 2 groups (not shown). The loss of eyelash reflex occurred faster in the sevoflurane group (35 ± 3 sec vs 56 ± 5 sec, $p < 0.05$). No ventilatory adverse events occurred at induction and were of same incidence during the maintenance of anaesthesia. The mean arterial pressures were not different between groups but the heart rate was slower in group S during anaesthesia (not shown). 14/26 patients moved during anaesthesia in group P whereas only 4/26 in group S ($p < 0.05$). The incidence of postoperative vomiting was increased in the sevoflurane group ($p < 0.05$) The patients felt able to perform a normal activity after the same delay (18.4 ± 2.9 H vs. 20.6 ± 2.8 H, $p > 0.05$) and the percentage of unpleasant feeling in the per and postoperative period was the same between groups. The total cost of anaesthesia (syringe, anaesthetic agents and medical gases) was lower in group S (679 FF for 24 patients vs. 1153 FF for 25 patients). Four patients had to be reoperated in group S because of uterine haemorrhage (none in group P) The weight of aspiration product in the last 26 patients was higher in group S (293 ± 66 g) as compared to group P (108 ± 8 g, $p = 0.004$).

Discussion & Conclusion: The single breath induction with 8% sevoflurane allows a faster induction and a more reliable depth of anaesthesia when associated to premedication and opioids. Emesis was more frequent in group S but of short duration which did not preclude the discharge of the patient nor their return to a normal activity The risk of uterine haemorrhage is of concern in patients receiving sevoflurane and further investigations concerning blood loss in obstetrics are warranted. For other ambulatory, surgery, anaesthesia with sevoflurane is a good alternative to propofol

A.39 Postoperative nausea and vomiting in day-case arthroscopy patients

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Background and Goal of Study: We have studied the effects of 2 different inhalational agents in arthroscopy surgery in order to quantify the differences in nausea and vomiting.

Materials and Methods: After ethical committee approval and informed consent 156 ASA I–II patients, undergoing day-case arthroscopy surgery were allocated to a balanced anaesthetic technique, differing only in the type of volatile agent utilised Patients were induced intravenously with propofol (3–4 mg/kg) and fentanyl (1–1.5 μg/kg). Then utilising a spontaneously ventilating technique the patient was exposed to either desflurane (76 patients) or isoflurane (80 patients) in 33% oxygen and nitrous oxide. Pain, nausea and vomiting were assessed. The categorical data was analysed with a Chi-square test and contingency table (statistical significance if p-value was less than 0.05).

Results and Discussion: 18 patients experienced postoperative nausea, 14 of these were in the desflurane and 4 in the isoflurane group of patients ($p < 0.05$). The recovery profile of desflurane has been previously studied in a variety of settings (1, 2). Whilst nausea has been previously reported as an incidental finding (3), our study shows a clear association with desflurane compared with isoflurane.

Conclusion: This study shows a significantly higher incidence of PONV in the patients receiving desflurane compared with isoflurane in a day-case population undergoing knee arthroscopy.

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A.40 Propofol autocoinduction in ambulatory anaesthesia

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Background & Goal of Study: Propofol as the sole induction agent significantly decreases arterial blood pressure. Addition of midazolam reduces the induction dose of propofol[1] but delays psychomotor recovery of patients in postoperative period[2]. The aim of this study was to compare post-induction haemodynamic effects and recovery times from anaesthesia using three different co-induction techniques.

Material & Methods: 36 ASA I & II outpatients admitted for minor orthopaedic surgery were randomly allocated to receive alfentanil 10 $\mu g.kg^{-1}$ 2 min prior to induction followed by either midazolam (M) 0.05 $mg.kg^{-1}$ or propofol (P) 0.4 $mg.kg^{-1}$ or saline (S) 2 ml. After 2 min P infusion was commenced at a rate of 50 $mg.kg.^{-1}h^{-1}$ until loss of eyelash reflex. Laryngeal mask airway (LMA) was inserted. Mean arterial blood pressure (MABP) was noted at 1 min intervals starting before the first injection until LMA was in situ. Anaesthesia was maintained with O_2/N_2O/Isoflurane. Times for eye-opening after surgery (EOAS) and discharge-readiness (DR) were recorded. The maximum percentage reduction in MABP was calculated. Data was analysed using ANOVA ($p < 0.05$). Results are expressed as mean values ± standard deviation.

Results & Discussion: All groups were comparable for age, sex, weight, ASA status and duration of surgery. There was significant difference between the groups in total dose of P required, reduction of MABP following induction of anaesthesia and discharge readiness from hospital in favour of the auto-co-induction i.e. P + P technique (table 1).

Table 1

Variables/Groups	S + P	P + P	M + P
Reduction in MABP (%)	22 ± 4.7	14 ± 3.2	15 ± 3.6
Time EOAS to DR (min)	142 ± 16	124 ± 11	174 ± 24
Dose of P per patient (mg)	183 ± 25	129 ± 17	105 ± 25
Cost per induction/patient	£3.55	£2.5	£2.3

Conclusions: P + P reduced undesirable cardiovascular effects of S + P, shortened discharge times from the hospital compared to M + P and reduced overall cost per patient.

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A.41 Remifentanil *vs* fentanyl in ultrashort gynaecological day surgery

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Background and Goal of Study: Remifentanil (Remi) is an esterase metabolized opioid with a short elimination half-life (1) (2). The purpose of this preliminary study (Institutional approval request) is to verify if Remi may be used, in single-shot administration, so to obtain a good analgesia free from side effects in cases of gynaecological day-surgery not exceeding 10 min.

Materials and Methods: Fourty patients similar in terms of age, height, weight, ASA status, duration and type of surgery were randomized (double blind) into two Groups: Remi or Fentanyl (Fenta). The patients, pre-medicated with 0.4 mg of atropine, and pre-oxygeneted for 3 min., have been anaesthetized by bolus of propofol as follows: 50 mg in bolus + 10 mg every 10 sec. up to loss of consciousness. In the first Group analgesia has been secured by Remi in dosage 1 μg/kg (3); in the second by Fenta 1.5 μg/kg. Further doses of propofol have been administered when needed. All patients underwent surgery, in spontaneous breathing, while being monitorized on ECG, FC, PAS, PAD, PAM, Sat. O_2. Time of emergence was registered, together with presence or absence of anaesthesia side effects; pain was mesured by VRS both at emergence and after 30 min.

Results and Discussion: Emodynamic stability has resulted analogous in both Groups; Sat. O_2 has never appeared inferior to 97%. Group Remi has been administered a lower dose of propofol. As the Table shows, emergence and recovery of mental performance intervened slightly earlier in Group Remi. Post-operatory pain detected by VRS has proven more intense in the Remi Group, in accordance with its half-life.

	Remifentanil	Fentanyl
Operation length	9.4 ± 3.15*	10.15 ± 2.39*
Propofol used	169 ± 25*	189 ± 32*
Eyes opening	2.5 ± 1.76*	2.4 ± 2.16*
Reply to order	2.5 ± 1.67*	2.8 ± 2.12*
Date of birth	2.95 ± 1.95*	3.58 ± 2.12*
Discharge operatory room	5.23 ± 2.40*	6.01 ± 3.20*
Pain at emergence	1.1 ± 0.8**	0.2 ± 0.4**
Pain after 30 min.	1.5 ± 1.0**	1 ± 0.9**
Post-operatory nausea	1 case	2 cases

*mean and standard deviation **VRS

Conclusions: Our results indicate that analgesia induced by Remi in single-shot proves satisfactory in ultra-short surgicals operations.

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A.42 Target-controlled remifentanil in combination with propofol for spontaneously breathing day case patients: effects on respiration

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Background and Goal of Study: Remifentanil is a new ultra short acting opioid. As with other potent opioids it causes a dose dependent respiratory depression[1]. We, therefore, aimed to establish an appropriate range of target plasma concentrations which would allow anaesthesia, with adequate spontaneous respiration, in combination with propofol in a day case setting.

Materials and Methods: 20 unpremedicated adult patients undergoing day case surgical procedures were studied. A target-controlled infusion of remifentanil (concentration 20 μgml^{-1}) was started at a target concentration of 1.6 $ngml^{-1}$ and anaesthesia induced with a target-controlled infusion of propofol. A laryngeal mask was inserted and ventilation assisted as required to maintain an end tidal CO_2 ($EtCO_2$) between 6.5–7.0 kPa and an arterial oxygen saturation >95%. After surgical incision the propofol target was reduced to 4.5 μgml^{-1} and the remifentanil target concentration increased or decreased in increments of 0.2 $ngml^{-1}$ until adequate spontaneous ventilation to an $EtCO_2$ 6.5–7.0 kPa was achieved for a period of at least 5 minutes. The target plasma concentration of remifentanil which achieved this was noted.

Results: In only 12 of the patients studied was adequate spontaneous ventilation maintained for a full 5 minute period. In this group the target remifentanil concentration ranged from 0.6–2.8 $ngml^{-1}$ with a median of 1.6 $ngml^{-1}$ (Fig). This corresponded to infusion rates of 0.019–0.107 $\mu gkg^{-1}\ min^{-1}$ with a median of 0.050 $\mu gkg^{-1}\ min^{-1}$.

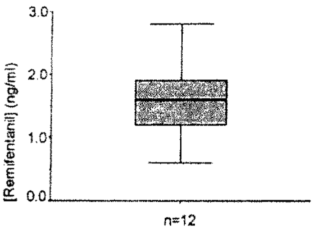

Fig. remifentanil target plasma conc ng/ml
median; interquartile range; range

Conclusions: Adequate spontaneous respiration using a combination of target-controlled remifentanil and propofol proved to be a difficult technique with only a 60% success rate, within the constraints of our protocol. The range of target concentrations which achieved this varied over a 4.7 fold range around a median of 1.6 $ngml^{-1}$. A controlled ventilatory technique might, therefore, be more appropriate.

References

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A.43 Rapid recovery from anaesthesia with remifentanil and isoflurane, enflurane or propofol may enable more inpatient, short surgical procedures to be performed as day-cases

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Background and Goals of Study: Remifentanil (R), is a highly potent, μ-receptor selective, esterase-metabolised opioid with a half-life of 8–10 minutes[1]. This international study investigated the effects of R with isoflurane (I), propofol (P) or enflurane (E) upon the quality of anaesthesia and recovery in day-case or in-patients undergoing identical surgical procedures. Because of R's short duration, post-operative nausea and vomiting (PONV) was additionally assessed. The intra-operative outcomes have been presented elsewhere.

Materials and Methods: Following ethics approval and signed consent, 854 patients (445 day-case and 409 in-patients), ASA class I–III undergoing gynaecological laparoscopy, varicose vein or arthroscopic surgery were randomised to R & I, R & E or R & P. Induction proceeded with R and P followed by routine muscle relaxation. After tracheal intubation, anaesthesia was maintained with R infusion and I or E at 0.5 MAC or R and P infusion at 100 μg/kg/min. Intra-operative NSAID ± wound infiltration with local anaesthetic provided post-operative analgesia. PONV was managed with routine anti-emetics.

Results and Discussion: Extubation and recovery of respiratory function occurred within median times of 5–7 minutes after end of anaesthesia. PONV, recovery room (RR) and hospital (Hosp.) discharge results are presented below

Endpoints (All times in minutes)	R + I (N = 285)	R + E (N = 285)	R + P (N = 284)
Median anaesthesia duration	53	53	52
Anti-emetics Day/In-Pt (%)	16/15	17/21	5/14
Day Patients – Median time	(N = 148)	(N = 149)	(N = 148)
RR discharge qualification	34	35	30
Actual RR discharge	75	72	76
Hosp discharge qualification	161	167	146
Actual Hosp discharge	248	225	228
Nausea (%)/Vomiting (%)	19/8	17/9	13/3
In-patients – Median time.	(N = 137)	(N = 136)	(N = 136)
RR discharge qualification	35	37	36
Actual RR discharge	68	64	66
Hosp discharge qualification	1319	1250	1211
Actual Hosp discharge	1773	2592	1797
Nausea (%)/Vomiting	24/15	23/13	11/31

Conclusions: R with I, E or P provided extremely stable anaesthesia and consistent recovery. PONV was much lower in the R&P group suggesting this combination may be useful in patients at risk of developing these symptoms. The consistently short RR discharge times for day-case and in-patients suggests that more institutions may be able to consider accommodating current, in-patient, short surgical procedures on a day-case basis.

Supported in part by a grant from Glaxo Wellcome

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A.44 Remifentanil and desflurane – an ideal combination for rapid recovery?

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Background and Goal: For clinical use the new opioid remifentanil must be combined with another anaesthetic agent. Propofol, well established for ambulatory anaesthesia, appears to be the first choice. However, the properties of desflurane (low blood-gas solubility, rapid elimination) suggest this volatile anaesthetic at least as a comparable alternative [1]. The goal of this study was to compare the recovery times after anaesthesia with remifentanil in combination with either propofol or desflurane.

Materials and Methods: With institutional approval and written informed consent 40 gynaecological patients (ASA status I–II) scheduled for elective laparoscopy were studied at random. All patients received 5 mg diazepam p.o. at least 1 h prior to surgery. Anaesthesia was induced with remifentanil 1 μg/kg followed by remifentanil infusion (0.5 μg/kg/min) and propofol 1–2 mg/kg. For maintenance remifentanil was reduced to 0.25 μg/kg/min five minutes after intubation and combined with either propofol 0.1 mg/kg/min or 0.5 MAC (3 vol%) desflurane in O_2/air With termination of surgery anaesthetic delivery was discontinued simultaneously and recovery times were recorded. Statistical significance ($p < 0.05$) was proved with Mann-Whitney-U-test, all data are presented as mean ± SEM.

Results: Both groups (desflurane n = 20, propofol n = 19) were comparable in respect of demographic data, anaesthetic dosages, and duration of anaesthesia and surgery Recovery times were significantly shorter for remifentanil desflurane than for remifentanil propofol.

Time to [min]	Remifentanil Desflurane	Remifentanil Propofol	p value
Spont ventilation	6.4 ± 0.6	9.6 ± 0.9	0.01
Extubation	6.7 ± 0.6	9.8 ± 0.9	0.02
Open eyes	6.5 ± 0.6	9.8 ± 0.9	0.01
State name	7.2 ± 0.6	10.6 ± 1.0	0.02
PACU arrival	11.1 ± 0.8	14.7 ± 1.0	0.005

Conclusions: Emergence after 0.25 μg/kg/min remifentanil is more rapid when combined with 0.5 MAC desflurane than with 0.1 mg/kg/min propofol Regarding the recovery times, this study demonstrates that desflurane is a suitable adjunct to remifentanil and an alternative to propofol, particularly for ambulatory anaesthesia. Differences are best explained by the pharmacological properties of both co-anaesthetics, their applied dosages, and their different interaction with remifentanil Clinical experience gained hitherto suggests that for both co-anaesthetics a further dose reduction is possible, depending on the surgical procedure

References

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A.45 Blood alcohol concentration and psychomotor effects on skills associated with driving

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Background & Goal of Study: Fitness to drive following ambulatory anaesthesia is a current topic of debate The only legal standard which exists for fitness to drive while under the influence of a drug is that of blood alcohol concentration (BAC) Our goals were to assess impairment occurring with intravenous infusions of alcohol at the 3 European legal standards of 20, 50 and 80 mg 100 ml^{-1} BAC and use this as a standard by which anaesthetics can be compared.

Materials & Methods: We compared an oral dose of alcohol 0.75 $mg.kg^{-1}$ with an intravenous infusion designed to achieve 20, 50 then 80 mg 100 ml^{-1} BAC in 12 healthy volunteers. Subjects were given 0.75 $ml.kg^{-1}$ alcohol diluted in fruit juice to drink and when their BAC decreased to 20 mg.100 ml^{-1} an infusion of 5% alcohol commenced. Breath analysis of BAC was used to control the infusion rate and maintain a steady BAC for 30 mins each at 20, 50 then 80 mg.100 ml^{-1}. Psychomotor performance was assessed by tests of choice reaction and a dual attention task. Parametric data were analysed using ANOVA. $P < 0.05$ was regarded as significant.

Results & Discussion: At the 20 mg. 100 ml^{-1} target the mean BAC was 22.1 mg.100 ml^{-1} (SD 3.7), at 50 mg 100 ml^{-1} it was 51.5 mg 100 ml^{-1} (SD 3.3 mg.100 ml^{-1}), and at 80 mg 100 ml^{-1} was 80.5 mg 100 ml^{-1} (SD 4.2 mg.100 ml^{-1}). This compared to the oral dose where the peak ranged from 19 to 68 mg.100 ml^{-1} In psychomotor testing, choice reaction time showed significant differences between the 50 and 80 mg 100 ml^{-1} conditions and baseline ($P < 0.05$) In dual task, secondary reaction time showed a statistically significant difference between all groups and baseline ($P < 0.05$) while tracking showed a significant difference between the 50 and 80 mg groups and baseline ($P < 0.05$)

Conclusion: Oral dose gives widely variable BACs which makes it difficult to make reliable assessments of impairment An intravenous infusion enables the investigator to maintain the blood alcohol concentration within a narrow range. This allows reliability and precision when investigating the effects of alcohol on psychomotor performance.

A.46 Blood propofol concentration and psychomotor effects on skills associated with driving

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Background & Goal of Study: Fitness to drive following ambulatory anaesthesia is an important issue. In previous work we have investigated the decrement in performance seen with blood alcohol concentration (BAC) at the 3 European legal permitted limits for driving of 20, 50 and 80 mg.100 ml^{-1}. The aim of this study was to compare impairment in psychomotor performance seen following propofol infusion with that occurring at the legal limits for driving under the influence of alcohol

Materials & Methods: Informed consent was obtained from 6 healthy volunteers and baseline recordings of psychomotor performance made. An infusion of propofol was commenced at a target concentration of 1 μg.ml^{-1} and increased incrementally until the subjects were heavily sedated. The target was then reduced and maintained at 0.8, 0.4 and 0.2 μg.ml^{-1} for 30 mins each while the subject performed 3 psychomotor tests which were repeated twice at each level. The tests employed were choice reaction time, dual task tracking with secondary reaction time and within list recognition memory. Parametric data were analysed using ANOVA and non-parametric using Krushall-Wallis. $P < 0.05$ was regarded as significant.

Results & Discussion: The propofol concentration required to produce sedation varied from 1.4–3 μg.ml^{-1}. ANOVA did not reveal any significant differences between the 3 doses of propofol using choice reaction time but examination of 95% confidence intervals revealed a difference between 0.8 μg.ml^{-1} and baseline. The mean deterioration at 0.8 μg.ml^{-1} was 107 ms^{-1} ($P < 0.05$). ANOVA revealed a significant difference between groups in secondary reaction time ($P < 0.05$). Subsequent analysis of confidence intervals revealed there to be a significant difference between 0.8 and 0.4 μg.ml^{-1} and baseline. The mean deterioration seen was 187 and 85 ms^{-1} respectively. The results presented here when compared to previous work with alcohol reveal a greater degree of impairment seen at 0.8 μg.ml^{-1} propofol than at a blood alcohol concentration of 80 mg.100 ml^{-1}. When the blood propofol falls to a target of 0.4 μg.ml^{-1} the impairment seen in psychomotor testing is less than observed at 50 mg.100 ml^{-1} BAC and at 0.2 it is less than even 20 mg.100 ml^{-1} BAC.

Conclusion: Low dose propofol caused minimal deterioration in psychomotor testing. The impairment seen was less than that observed at the permitted legal driving limits of 20, 50 & 80 mg.100 ml^{-1} (Sweden, France and UK respectively).

A.47 Assessment of balance using computerized dynamic posturography after day-case anaesthesia for nasal surgery

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Background & Goal to Study: Simple clinical tests of postural stability after day case surgery are inadequate when assessing the suitability of patients for discharge. Computerised dynamic posturography (CDP) is a technique which allows a quantified assessment of integrated balance control(1). The aim of the study was to assess balance prior to discharge using CDP in adult patients undergoing elective day case nasal surgery.

Materials & Methods: 22 patients were recruited and each received a standard anaesthetic of fentanyl 1 μ.kg^{-1}, propofol 2–3 mg.kg^{-1}, atracurium 0.5 mg.kg^{-1}, diclofenac 100 mg PR and an oxygen/nitrous oxide mixture with 1–1.5% isoflurane. Paired CDP study data was collected for each patient at baseline (pre-op), 1.5 hour and 3 hours after termination of anaesthesia. CDP testing consisted of a sensory organisation test (SOT) and the movement coordination test (MCT). The SOT consists of six stages:- 1) SOT1- eyes open with forceplate and visual surround fixed; 2) SOT2- eyes closed with forceplate fixed; 3) SOT3- eyes open with visual surround sway-referenced and forceplate fixed; 4) SOT4- eyes open with forceplate sway-referenced and visual surround fixed; 5) SOT5-eyes closed with forceplate sway-referenced; 6) SOT6- eyes open with visual surround and forceplate sway-referenced. Paired student's *t* test was used for statistical analysis of CDP data and $P < 0.05$ was considered significant.

Results & Discussion: Two patients had to withdraw from the study due to post-operative nasal haemorrhage. No significant difference was detected between the baseline versus the 1.5 or 3 hour SOT equilibrium scores (%) and the MCT latencies (ms).

	Baseline	1.5 hour	3 hours
SOT1	95.4 ± 1.8	94.9 ± 2.1	95.3 ± 1.6
SOT2	92.8 ± 3.0	91.8 ± 3.3	93.1 ± 2.6
SOT3	89.9 ± 4.3	86.9 ± 6.3	88.7 ± 4.1
SOT4	85.9 ± 6.7	86.5 ± 7.2	87.9 ± 6.8
SOT5	67.8 ± 10.8	65.5 ± 11.4	71.0 ± 8.0
SOT6	62.5 ± 12.0	64.2 ± 15.2	67.5 ± 10.6
MCT	149.0 ± 15.7	148.2 ± 13.2	143.8 ± 10.7

Conclusion: In day case nasal surgery patients receiving a standard anaesthetic technique, CDP testing failed to detect any significant impairment of integrated balance control at 1.5 and 3 hours post-operation.

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A.48 Predicting factors from unanticipated admission following ambulatory surgery

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Background and Goal of the Study: Hospital admission following ambulatory surgery is a valid measure of morbidity and a quality indicator. To improve the adecuate direction of an ambulatory surgery unit it is essential to study that factors associated with unexpected hospital admission. Our goal was to analyze the association of age, ASA, type of surgical and anesthetic procedures, surgical duration, pain, vomiting and surgical and anesthetic complications with unexpected admission following ambulatory surgery in our setting.

Methods: Design used was retrospective case-control study for the reason that, unexpected hospital admission is a rare event. The subjects studied were, all patients subjected to ambulatory surgery in the Viladecans Hospital from October 1990 till May 1996 (N = 6071). This cases ($n_1 = 93$) were obtained from admission records for ambulatory surgery. Controls ($n_0 = 552$) were selected at random from all patients without being admitted. Logistic regression models with a predicative variable and multiple logistic regression were obtained Odds Ratio and its corresponding 95% CI were calculated in order to analyze the relationship between risk factors and hospital admission.

Results and Discussion: Our results agree with Gold[1] according to surgery time, emesis and divergence according to age, ASA and general anaestesia.

Association of factors with admission. Initial logistic analysis/multiple logistic regression

Factor	Odds Ratio initial/multiple regression logistic	95% CI initial/multiple regression logistic
Age	0.99	0.9–1.9
ASA > I	0.99/3.44*	0.4–2.2/1.36–0.072
Laparoscopy	6.51*/1.01	2.2–19/0.12–8.27
Abdominal surgery	5.06*/0.76	1.7–14/0.08–7.54
Proctological surgery	5.61*/34.64*	1.9–16/3.94–304
21 to 40 minutes	8.29*	2.44–28
> to 41 minutes	7.44*/22.37*	3.7–14/5.33–93
TIVA	6.80*/3.31	3.6–12/0.39–27.9
Inhalatory	1.66/0.6	0.6–4/0.04–9.9
Rachidian anaesthesia	2.69*/1.01	1.2–5.7/0.19–5.2
Rachidian anaesthesia with profound sedation	20.76*/19.9*	8.9–48/3.25–122
Dolor	17.42*/12.4*	6.9–43/2.79–55
Vomiting	5.37*/8.4*	1.7–16/1.21–59
Surgery complication	37.6*/58.0*	19–73/20–165
Anesthetic complicat.	35.1*/138*	11.6–106/26–729

*$p < 0.01$

Conclusions: surgical and anesthetic complications, proctological surgery, rachidian anaesthesia with profound sedation, pain and surgery time more than 40 minutes were main predictting factors for unexpected admission in ambulatory surgery.

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A.49 Patients' experiences of day surgery

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Background & Coal of Study: Day surgery patients are well followed concerning pain and nausea during their stay at the hospital, but little is known after they leave the unit. To assess the quality of our care and patients' overall satisfaction we made a survey.

Patients & Methods: 217 patients were randomly selected for a telephone interview by an anaesthesiologist on the following day. Patients were asked about the presence and intensity of nausea, vomiting and pain or any other untoward symptom, use of pain medication and overall satisfaction of their experience. An 11- point rating scale (0–10) was used for assessment of nausea and pain.

Results: Ten patients (4.6%) of the original study group were admitted to the hospital. Four patients were not reached by phone. Thus the survey was completed with 203 patients.

65% had orthopaedic lower limb surgery, 11% hand surgery and 24% general surgery. 54% were women and 46% men. 85.7% had ASA 1 and 12.3% ASA 2 status. Spinal anaesthesia was used in 65%, general in 21%, intravenous regional anaesthesia in 10% and brachial plexus, epidural or local infiltration anaesthesia in 4%. Nausea was experienced by 5.9% of all patients during their stay at the hospital, one patient was vomiting Tree patients were treated with antiemetics. After discharge 12 patients (6%) had experienced nausea. Only one had taken antiemetic medication at home. 11.3% (23.3% after general and 6.8% after spinal anaesthesia) had nausea during their whole day surgery experience.

21 patients (10.3%) had no pain during the first 24 hours after discharge 10 patients (4.5%) rated their overall pain very severe (point 9 or 10). At the time of the interview 63 patients (31%) had no pain, three patients still rated pain very severe. 28.1% had taken no pain medication 27 patients had headache after discharge. 22 of these had had spinal anaesthesia, 3 needed blood-patch 14 patients (0.6%) after spinal anaesthesia reported spontaneously pain in the lower limbs or back.

182 patients were very pleased and 21 fairly pleased to their day surgery experience None of the patients was dissatisfied.

Conclusions: During the first 24 hours after discharge most of the patients were pleased and feeling well with only little discomfort Nausea and vomiting was not a problem, but postoperative pain treatment needs further evaluation The provision of analgesics and adequate information for their use at home is crucial for all patients

A.50 Day case laparoscopic cholecystectomy: the anaesthetic experience

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Background & Goal of Study: Laparoscopic cholecystectomy is increasingly being performed as day case surgery. This study reviewed the anaesthetic method and experiences of patients after hospital discharge to determine if this is safe, feasible and acceptable.

Materials & Methods: Unselected patients taken from one surgical waiting list were booked for day case laparoscopic cholecystectomy Each patient was routinely screened pre-operatively by nursing staff. The surgery was performed by a consultant surgeon and two higher surgical trainees

A standardised anaesthetic technique was used: premedication with temazepam, metoclopramide and ranitidine if required; induction with glycopyrrolate, midazolam, fentanyl, propofol, ondansetron; intubation using atracurium, and maintenance with isoflurane and 66% nitrous oxide in oxygen. A nasogastric tube was inserted Two litres of iv fluids were given Analgesia included 100 mg diclofenac and 1 g paracetamol PR with additional fentanyl as required and 0.5% plain bupivacaine to the port sites. Post-operatively further diclofenac was given and if necessary one dose of IM morphine, followed by oral analgesia

Patients were discharged by the nurses using standardised criteria and given written and verbal information The patients were telephoned on the day after surgery and followed up one week later

Results & Discussion: A total of 60 patients (one was unsuitable due to unstable diabetes) were studied over 5 months The average age was 52 years

Mean surgical time was 62 minutes (26 to 166) The average time to discharge was 6 hr 2 min There were 11 overnight admissions (18%); 3 anaesthetic, 4 surgical (one open cholecystectomy) and 4 social admissions One patient was re-admitted for a retained stone

10 (21%) of those who had been day cases said that they would have preferred an overnight stay.

Average post-operative use of co-proxamol was ten tablets

Conclusions: This study demonstrated that by use of a standardised anaesthetic technique including multimodal analgesia, laparoscopic cholecystectomy can be successfully and safely carried out as a day case with a high degree of patient satisfaction. Overnight facilities should however be available

A.51 Bispectral analysis of the EEG to compare the hypnotic effects of inhalation (sevoflurane) *vs* intravenous (propofol) anaesthesia induction in day surgery patients

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Previous studies revealed that an empirically derived bispectral EEG measure, the bispectral index (BIS), is a significant predictor of depth of anesthesia. The goal of this study was to compare pharmacodynamic characteristics of induction (rapidity of onset and depth of anesthesia) of inhalation vs intravenous anesthesia as measured by bispectral index

Methods: Following local ethical committee approval, sixty, unpremedicated ASA I or II patients, aged 18 to 70 years, scheduled to undergo elective hysteroscopic procedures were studied Patients were randomly allocated to receive inhalation or intravenous anesthesia induction For inhalation induction, a deep breath inhalation induction with sevoflurane was applied. After priming of the respiratory circuit and after a deep expiration, patients were asked to inhale deeply 8% sevoflurane in a mixture of O2/N2O (35/65%) For intravenous induction of anesthesia, propofol 2.5 mg/kg bw was injected over a 15 sec period Bispectral EEG monitoring was performed in a bifrontal referential montage using an Aspect-1000 EEG monitor.

Results: Both groups were demographically similar with no differences between them in terms of age, weight or heigth The time to loss of consciousness in the pts receiving propofol (mean 57 sec SD 13 sec) was not statistically different from pts receiving inhalation induction with 8% sevoflurane (mean 48 sec SD 17 sec) In both groups, the decrease in BIS started at the same time as the loss of consciousness, with the minimal BIS occurring at a mean of 40 sec later Comparing the depth of induced anesthesia, by comparing the minimal BIS values, there was no significant difference between intravenous and inhalation induction (propofol mean BIS 32, SD 14, sevoflurane: mean BIS 28, SD 12)

Conclusion: Bispectral EEG analysis revealed that 8% sevoflurane deep breath inhalation offers equal conditions of anesthesia induction (concerning onset and depth of anesthesia) as intravenous propofol induction.

A.52 Comparison of three methods of inhalation induction with sevoflurane in adults

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Background and Goal of Study: This multicenter study compares 3 induction methods with sevoflurane in nitrous oxide 66%. Different concentrations (8%, 4.5%[1]) with the vital capacity (VC) method and incremental induction (1% increase every 3 breaths) at normal tidal volume (ITV)

Materials and Methods: After Ethics Committee approval, written informed consent was given by 121 adult ASA I–II patients undergoing short procedures (<90 min). Fentanyl (1 μg/kg iv) was given before induction Patients randomly received VC8, VC4.5 (prefilled circuit, Philip et al [2,3]) or ITV After loss of lash reflex, sevoflurane was fixed at 4.5% until LMA placement. Times to loss of lash reflex and voluntary movement were assessed. Side effects and easiness of LMA insertion were recorded After, patients evaluated quality of induction Values of $p < 0.05$ were considered as statistically significant (* in table below)

Results and Discussion:

Table 1 Time to induction indicators, seconds [mean ± SE]

Group	N	Lash reflex	Voluntary movement
VC8	42	67.9 ± 7*	62.3 ± 7.5*
VC4.5	39	98 ± 7.5	88.3 ± 7*
ITV	40	115.7 ± 6.1	111.9 ± 6.1*

There were no significant differences in time to loss of lash reflex between VC4.5 and ITV, but the ANOVA (Bonferroni correction) shows tendencies in that direction. 19% of patients had side effects; most frequent were secretions (8.2%) and excitement (5.7%), with no significant differences between groups

LMA insertion was easy in 85.1% of cases Only 6.7% considered induction unpleasant, and 94.2% would repeat the same technique (no significant differences between groups). There were no hypoxic episodes ($SpO_2 < 90\%$)

Conclusion: VC8 is the fastest method, with no increase in side effects More time is needed to instruct the patient and prefill the circuit Induction with sevoflurane in adults, with any of the three described methods, is fast and safe. It permits easy placement of LMA and provides a high degree of patient satisfaction.

Supported by Abbott Laboratories, S A (Spain).

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A.53 Cost minimization comparison of sevoflurane compared with propofol and isoflurane in gynaecological day-case surgery

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Background: The use of the propofol for induction coupled with isoflurane are currently the most commonly used agents for day surgery. Sevoflurane is readily acceptable for inhalational induction as well as maintenance[1] The purpose of this study was to compare the costs of sevoflurane only with a propofol isoflurane technique and relate these to advantages for both patients (morbidity, acceptability) and the hospital (anaesthesia and recovery times).

Methods: 40 ASA I–II patients undergoing gynaecological day surgery were randomly allocated to induction/maintenance with propofol/isoflurane or sevoflurane/sevoflurane according to a protocol approved by the hospital ethics committee. All patients received fentanyl 1 mcg kg^{-1} Anaesthesia was induced with either propofol 2 5 mg kg^{-1} or inhalation of sevoflurane 8% in O_2 30% and N_2O 60% Propofol patients had anaesthesia maintained with isoflurane 0.6–4%. Sevoflurane patients had this agent continued at 1–4%. Patients breathed spontaneously via an LMA and a circle system (gas flow 21 min^{-1}). Induction and emergence times as well as complications were recorded peri-operatively Costs of all anaesthetic agents and disposables were calculated based on NHS list prices Data (mean values and SD) were analysed by either the Mann-Whitney "U" test or a two sample t-test with $p < 0.05$ considered significant (*)

Results: The two groups were comparable with respect to age, weight, height, ASA status, and duration of anaesthesia. Induction with sevoflurane was slower when compared to propofol (Table)

	Propofol/isoflurane	Sevoflurane
Number	20	19
Induction time (min)	1 07 (0 37)	1 43 (0 41)*
Recovery time (min)	7.11 (2 52)	6 13 (1 28)
Total cost	£11 55 (4 64)	£13 28 (5 29)

Conclusions: The cost of induction and maintenance of anaesthesia with sevoflurane in patients undergoing gynaecological day surgery is similar to propofol and isoflurane.

Acknowledgement: This work was supported by Abbott Laboratories Clinical Research Department

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A.54 The ingestion of caffeine and the appearance of headache postoperatively or after an endoscopy or an x-ray procedure

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Objective: To determine the importance of caffeine withdrawal in the complaint of headache postoperatively, or after X-ray or endoscopy procedures.

Material and Methods: We have studied 444 patients (286 men and 158 women mean age 56 ± 11 years) before and after having done a simple surgical or roentgenographic procedure or an endoscopy of upper or lower gastrointestinal tract. All patients have completed a questionnaire survey that included information of. a) on usual habit of caffeine intake, b) the caffeine use before or after the surgical, X-ray procedure or endoscopy, and c) the presence and severity of their headache accordingly.

Results: Analyzing the given answers we have found that 89% of our patients drink caffeinated beverages twice or more daily. Among regular caffeine users, 35% experienced a headache after the surgical, X-ray or endoscopy procedure compared to 11% of nonusers Among the most of heavy caffeine consumers who have abstained from beverages on the day of their procedure, 45% experienced a headache. Our final study data indicated that the use of caffeinated beverages on the previous day of the above procedures effectively prevented the headache.

Conclusions: The caffeine withdrawal is an important cause for postoperative headache, it may also cause headache in patients who are not doing surgical procedures, such as roentgenographic procedures, and endoscopy of upper and lower gastrointestinal tract

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A.55 Spinal anaesthesia with hyperbaric bupivacaine 0.1% in ambulatory perineal surgery

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Background & Goal of Study: To compare the "saddle" subarachnoid block for perineal surgery, using either 0.1% (target) or 0.5% (control) bupivacaine

Material & Methods: 48 patients scheduled for elective surgery were included The technique was performed with a 27G Whitacre needle, in the interspace L4–L5. After injection of the anesthetic solution, the patient remained in the sitting position for 5 minutes. According to the anesthetic solution, two groups were formed. A group (control), using 2 ml of 0.5% hyperbaric bupivacaine (10 mg), and B group with 4 ml 0.1% hyperbaric bupivacaine (solution obtained from mixing 4 ml plain 0.5% bupivacaine and 4 ml 5% dextrose). Both the sensitive (needle punctioning) and the motor (BROMAGE scale) blockade degree were evaluated at the beginning and end of surgery, as well as 1 hour after surgery end The patient's ability to walk 1 hour after surgery, and the time needed for discharge were also accounted Statistical analysis was performed using the t-Student for parametric data, considering a p value of less than 5%

Results and Discussion: Intraoperatory period: All patients in both groups presented an adequate sensitive blockade. 66% of the patients in the B group presented no motor blockade, whereas all patients in the control group did ($p < 0\ 05$)

Postoperatory period: The motor blockade degree was 3 in all patients of the A group, against 0.6% in the B group ($p < 0.05$) in which 84% of the patients had a 0 or 1 degree. Only a 7% of the patients in the A group were able to walk 1 hour after surgery end, compared with 67% in the B group ($p < 0\ 001$) The most frequent postoperatory complication was urinary retention requiring bladder catheter in 20% of the patients of the A group, against only 9% in group B. The time required for accomplishing requisites for hospital discharge was 287.77 ± 103 11 minutes (mean/SD) in the A group, and 126.7 ± 66 2 minutes in the control group.

Conclusions: We conclude that the use of hyperbaric 0.1% bupivacaine is an effective technique for perineal ambulatory surgery, as the degree of motor blockade is low, therefore allowing rapid mobilization and presenting a lower incidence of adverse effects. The time needed for hospital discharge is significantly lower in the B (studied) group, an important factor for patients undergoing ambulatory surgery

A.56 Comparison of rocuronium and mivacurium during outpatient surgery: propofol *vs* sevoflurane

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Introduction: Short or medium acting non-depolarising muscle relaxants are preferred during outpatient surgery. Volatile agents increase the neuromuscular blocking potency of muscle relaxants The aim of this study was to compare the clinical duration of action and the recovery index between rocuronium (ROC) and mivacurium (MIV) under propofol (PRO) or sevoflurane (SEV) anaesthesia.

Methods: After IRB approval 60 consenting ASA 1–2 patients were randomly assigned to one of four groups; group 1 ROC-PRO, group 2. MIV-PRO, group 3. ROC-SEV, group 4. MIV-SEV. No premedication was used. Anaesthesia was induced with 0.2 μ/kg sufentanil and 2.5 mg/kg PRO We monitored neuromuscular function by accelerometry (TOF-Guard®), stimulating the ulnar nerve at the wrist After a stable twitch response, a single IV bolus of 0.4 mg/kg ROC in group 1 and 3 or 0 2 mg/kg MIV in group 2 and 4 was administered. Anaesthesia was maintained under N20/02 (70%/30%), with a 10 mg/kg/h PRO infusion rate (groups 1 + 2), and with sevoflurane starting with 2–2 2% (groups 3 + 4), adjusted later to a combined nitrous oxide volatile agent end-tidal concentration between 1 and 1 2 MAC For all groups, time to 90% neuromuscular bloc (nmb90), duration 25%, 75% and 90% (time to 25%, 75% and 90% recovery of T1) and the recovery index 25–75% were measured. Data were analysed using ANOVA and DUNETT T3 multiple range test with $p < 0\ 05$ considered significant

Results: The four groups were demographically comparable. The nmb90 time was shorter in groups ROC compare to groups MIV but the difference was only statistically significant for the group ROC-SEV. The duration 25%, 75% and 90% in group 3 were significantly longer than with other groups No difference was seen for the recovery index 25–75% but we found, in group 3, an important dispersion with a less predictable speed of recovery Mean ± SD; (range)

	Group 1 ROC-PRO	Group 2 MIV-PRO	Group 3 ROC-SEV	Group 4 MIV-SEV
Number (n)	15	15	15	15
nmb90 (sec)	132 ± 44	178 ± 57	108 ± 33*	181 ± 80
Duration 25% (min)	19 2 ± 4 1 (14–27)	15 2 ± 3 1 (12–21)	25 8 ± 5.3§ (18–35)	17 ± 3 7 (11–23)
Duration 75% (min)	25 9 ± 4 8 (17–32)	20 ± 4 (16–27)	35 4 ± 9 9$^{\#}$ (22–51)	22 7 ± 5 4 (15–34)
Duration 90% (min)	29 ± 6 1 (20–40)	23 5 ± 4 5 (17.5–31)	38.8 ± 11$^{\&}$ (25–57)	25 1 ± 5 9 (16–39)
Recovery 25–75 (min)	6 6 ± 2.6 (3–13)	5 ± 1 4 (3–8 5)	9 5 ± 6 4 (2 5–23 8)	5 6 ± 2 (3–11 5)

(*$p < 0\ 05$ compared to groups 2–4, §, $^{\#}$, $^{\&}$ $p < 0\ 05$ compared to groups 1–2–4)

Conclusion: The clinical duration of action after 0.4 mg/kg ROC was of 20 min. under PRO. Because of the greater potentiation of ROC by SEV and its less predictable duration, we do not recommend the use of ROC with SEV for outpatient surgery during short procedures

A.57 Effect on postoperative nausea and vomiting by antagonizing neuromuscular block

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Background: Concerns regarding the possible side effects of neuromuscular reversal drugs have increased interest in the use of short acting non-depolarizing drugs in the outpatient setting. There is conflicting evidence regarding the emetic properties of the neostigmine reversal of these drugs and the availability of mivacurium has made spontaneous recovery after neuromuscular block possible even in short surgical procedures.

Aim of the Study: We compared the effect on postoperative nausea and vomiting (PONV) in anesthesia for day-care surgery by using, in a randomized fashion, rocuronium with neostigmine reversal and mivacurium without reversal of the neuromuscular block.

Methods: We randomized 72 female patients scheduled for lower abdominal laparoscopy under general anesthesia to receive neuromuscular blockade by either rocuronium 0 4 mg × kg^{-1} and intubation after 120 sec or mivacurium 0 2 mg × kg^{-1} and intubation after 150 sec The rocuronium patients were reversed at the end of procedure using glycopyrrolate/neostigmine 0.5/2.5 mg and the patients relaxed with mivacurium recovered spontaneously. Conditions for intubation were graded on a four-point scale, and the neuromuscular block during procedure was assessed in all patients using a TOF-Watch® and patients were not extubated until there was a T4/T1-ratio of 90% All patients received a standard pentothal-fentanyl-isoflurane anesthesia and no anti-emetic drugs were given during anesthesia The occurance of PONV in the post anesthesia care unit (PACU) was registered and all patients were followed up with a questionnaire during 24 hours postoperatively

Results: Five patients were excluded because of conversion of surgery to laparotomy or need for reversal of mivacurium Intubating conditions were graded as excellent-good in 92% in the mivacurium group and 94% in the rocuronium group. The frequency of PONV in the PACU was 26% in the rocuronium group and 36% in the mivacurium group respectively ($p > 0.25$) Data from the 24 h follow up are to date incomplete and will be presented later

Conclusions: We found no difference in intubating conditions between the two drugs There was no statistically significant difference between the groups concerning PONV in the immediate postoperative period. To summarize our data do not substantiate the avoidance of neostigmine reversal of neuromuscular block in order to decrease PONV in the postoperative period.

A.58 Patient-maintained propofol sedation for premedication in day case anaesthesia

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Background and Goal of Study: High levels of state anxiety are commonly experienced by patients prior to surgery[1] However, standard premedication drugs can delay recovery and "home readiness" in patients undergoing day case anaesthesia[2] We aimed to assess the use of a patient maintained target-controlled infusion of propofol as a premedication prior to day case anaesthesia.

Materials and Methods: 20 adult patients undergoing day case surgical procedures under general anaesthesia were studied Anxiety was assessed using both a visual analogue scale (VAS) and the Spielberger State Trait Anxiety Inventory (STAI) Sedation was started pre-operatively with an intravenous target-controlled infusion of propofol at 1 μgml^{-1} The patient was able to increase the target concentration in increments of 0 2 μgml^{-1} by operating a control button Lockout time was 2 min and the maximum possible target concentration was 3 μgml^{-1}. If there were no demands within a set time the system decreased the target concentration in a stepwise manner Changes in anxiety scores were assessed relative to pre-sedation levels using the Wilcoxon rank sum test

Results: Mean duration of sedation was 43 1 min (range 30–72) There was a highly significant reduction in all median anxiety scores from 15 minutes after sedation was started Patients were generally lightly sedated Only 2 patients had a reduction in arterial oxygen saturation <94% and required supplementary oxygen via nasal cannulae There were no instances of airway obstruction. No clinically significant changes in heart rate or NIBP occurred Patient satisfaction, as assessed by a postoperative questionnaire, was high

Time (min)	STAI 20–80	VAS 0–100	Target [propofol] (μgml^{-1})
0	41 (33–62)	47 (33–62)	0
15	26 (23–30)*	24 (7–34)*	1 0 (0 8–1 4)
30	N/A	17 (1–24)*	1 2 (0 8–1 4)
AR	N/A	20 (5–28)*	1 2 (0 8–1 4)

Median (inter-quartile range) * $p < 0\ 0001$, AR = anaesthetic room, N/A = not assessed (n = 20) female male 14 6

Conclusions: Patient maintained propofol sedation provided a safe, rapid and highly effective anxiolytic premedication in patients undergoing day case anaesthesia

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Anaesthesia, day case, premedication*Sedation,* patient-maintained

A.59 Patient controlled sedation for colonoscopy

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Background and Goals: Benzodiazepines and opiate boluses are commonly used for colonoscopy with the attendant risk of respiratory depression (1) Patient controlled sedation (PCS) using propofol and alfentanil, allows titration of dosage to individual needs (2) We wished to compare these two methods for colonoscopy

Materials and Methods: 66 ASA 1 or 2 day case patients were enrolled. These were randomly allocated to either pethidine 50 mg and diazepam 10–20 mg bolus, dose decided by the endoscopist, (Group 1) or PCS (Group 2) using a Graseby 3300. The infusion contained propofol 10 mg/ml and alfentanil 25 μg/ml A 0.5 ml bolus could be self administered every 7 secs. 4 boluses were delivered early in the procedure then as needed All patient received 2 L/min O_2 were monitored and their sedation assessed. Number completion tests were timed pre and post procedure and patients followed up with a phone call 2 days later Mann-Whitney U tests, X^2 and t-tests were used as appropriate, $p < 0\ 05$ was taken as significant.

Results and Discussion: Group 1 received a median of 15 mg diazepam with pethidine 50 mg In group 2 there was a strong correlation between duration of procedure and dose ($r = 0\ 61$, $p < 0\ 0001$) Median (range) dose of PCS was 11 (2.5–22) mls and median (IQR) infusion rate was 6.25 (4 4–8.6) mg/kg/hr Duration of procedure was unaffected by the type of sedation PCS provided less sedation ($p = 0.0001$), less analgesia ($p = 0.004$) and recovery time was shorter with PCS, median (range) 10 (10–40) mins v 40 (10–240) mins in group 1 ($p = 0\ 0001$) Maximum fall in systolic BP was greater in group 1 Verbal contact was lost with 15 v 2 patients in group 1 and 2. 14 patients in group 1 had after effects disrupting lifestyle v. 3 in PCS group.

Conclusions: PCS provided lighter sedation, faster recovery times and less post procedure side effects, caused less fall in BP with no change in procedure duration or success rate but provided less analgesia than standard sedation

Acknowledgments: Supported by a grant from Zeneca Pharma

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A.60 Accuracy of waking time estimation after sedation by a computerized target-controlled infusion system

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Background & Goal of Study: Some computerized target-controlled infusion (TCI) systems calculate the time between stop of infusion and waking of the patient. The estimation can be influenced by changing the preset threshold drug level for awaking Using target concentrations ≥2 5 μg ml^{-1} for sedation in oral surgery, we wanted to find out whether a threshold of 2.4 μg ml^{-1} provides better estimates of waking time compared to a preset level of 1 2 μg ml^{-1}

Materials & Methods: For oral surgery 30 adults were sedated using propofol administered by TCI (Diprifusor®, Zeneca)[1] The threshold value for the estimation of waking time was adjusted to 1 2 μg ml^{-1} (group I, n = 15) or 2 4 μg ml^{-1} (group II, n = 15) The estimated waking time at the end of infusion and the time the patient actually needed to open his eyes and tell his name were registered The differences were verified with the Wilcoxon matched-pairs test

Results & Discussion: The mean actual waking time in seconds was 179 s ± 108 s (Mean ± SD). The difference between estimated and actual waking times was significant in group I ($p < 0\ 01$), but not in group II

	Total of propofol (mg)	Duration of TCI (s) (s)	Waking time (s)		Difference (s)
			estimated	actual	
I	614 1 ± 232 6	4068 ± 1815	1041 ± 589	176 ± 110	865 ± 578
II	713 7 ± 327 9	4640 ± 1957	131 ± 116	182 ± 110	108 ± 120

Mean ± SD

Conclusion: Using a propofol Diprifusor® system for sedation in oral surgery average waking times of about 3 minutes are usually to be expected. The estimation of the waking time should be based on a threshold value of 2.4 $\mu g \cdot ml^{-1}$ rather than on 1.2 $\mu g \cdot ml^{-1}$. Based on a threshold value of 2.4 $\mu g \cdot ml^{-1}$ waking times considerably different from 3 minutes may result from an inappropriate level of sedation.

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A.61 Inspired concentrations of desflurane and isoflurane required for equivalent rates of inhaled induction

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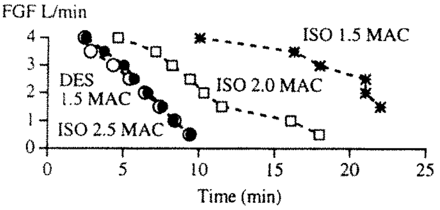
Background and Goal of Study: A potential advantage of inhaled anesthetics of low blood solubility is they allow change from high to low flow fresh gas flows (FGF) early in anesthesia while maintaining good control of the end-tidal anesthetic concentration (F_{et}). The aim was to determine how high the inspired concentration (F_i) ISO has to be to allow as rapid induction and achievement of low FGF as with low F_i DES.

Material and Methods: After IRB approval, we studied 28 ASA I or II patients, divided equally between four groups defined by the following delivered anesthetic concentrations (F_d): DES 1.5 MAC and ISO 1.5, 2.0 and 2.5 MAC. After tracheal intubation and with $P_{et}CO_2$ controlled between 35–40 mmHg, inhaled induction was done with FGF of 4.0 L/min O_2 and assigned anesthetic. When F_{et} DES or ISO reached 1.1 MAC, FGF was decreased by 0.5 L/min to 3.5 L/min while maintaining constant F_d DES or ISO. Successive 0.5 L/min decreases of FGF were made each time F_{et}DES or ISO reached 1.1 MAC. Median values and ranges are given.

Results and Discussion: Fet = 1.1 MAC was reached in 3.8 min (2–5.5) with DES 1.5 MAC, 2.4 min (1.5–3.0) with ISO 2.5 MAC, 4.6 min (2.0–7.5) with ISO 2.0 MAC and 18 min (5–38) with ISO 1.5 MAC. FGF could be decreased to low flow within 10 minutes without sag in F_{et} DES. Longer times at each FGF were required with ISO 1.5 MAC to allow F_{et} to rise to the target level before making the next decrease in FGF compared to with DES 1.5 MAC or ISO 2.5 MAC ($p < 0.05$) (Figure).



Conclusion: The times to achieve an anesthetizing F_{et} of DES or ISO were similar to reported values obtained under similar conditions. Only modest F_d overpressure leads to rapid induction and sustained F_{et} as FGF is decreased with DES whereas longer periods of higher F_d or FGF would be needed with ISO for rapid induction and stable F_{et}. ISO 2.5 MAC almost exactly resembled DES 1.5 MAC.

A.62 Cost minimization comparison of sevoflurane compared with propofol and isoflurane for the induction and maintenance of anaesthesia in day case surgery

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Background and Goal of the Study: Propofol and isoflurane are commonly used agents for day case anaesthesia. Recent studies comparing isoflurane with sevoflurane in out patients indicated improved recovery characteristics can be obtained in those patients who had maintenance of anaesthesia with sevoflurane [1, 2]. We have compared the costs of sevoflurane and propofol/isoflurane based induction and maintenance techniques and related these to patient morbidity, acceptability, anaesthesia and recovery times in a multi-centre hospital study.

Methods: Following local ethics committee and written consent, 186 patients (ASA I–II) scheduled for day case surgery in 7 NHS hospitals were randomly allocated to induction and maintenance with propofol/isoflurane (P/I) or sevoflurane/sevoflurane (S/S). Anaesthesia was induced with 1 mcg/kg fentanyl followed by either propofol (2.5 mg/kg iv) preceded by 1–2 ml of 1–2% lignocaine iv or by inhalation of sevoflurane 8% using a single vital capacity breath technique. Induction was timed to the loss of eyelash reflex. Patients in the propofol group had anaesthesia maintained with isoflurane 0.2–5.0% and those in the sevoflurane group continued with sevoflurane 0.5–8%. Both anaesthetic agents were administered during maintenance of anaesthesia using a laryngeal mask airway (LMA) with a rebreathing system at a flow rate of 1–2 L/min in 30–50% O_2 and 50–70% N_2O. Induction and emergence times as well as complications were recorded. The costs of isoflurane and sevoflurane, and all other anaesthetic agents and disposables were calculated from the NHS list price Data (mean, SD) were analysed by either the Mann Whitney "U" test or a two sample t-test with $p < 0.05$ considered significant (*).

Results: The two groups were similar with respect to patient characteristics, PONV and duration of anaesthesia. Induction with sevoflurane was slower compared with propofol, but recovery was faster with sevoflurane (table). The mean costs of induction and maintenance of day case anaesthesia in both groups were £10.63 (P/I) and £11.89 (S/S).

Table

Group	P/I	S/S
Cost (£)	10.63 (3.96)	11.89 (3.62)
Patients (n)	92	94
Induction time (min)	1.10 ± 0.53	1.43 ± 0.74*
Anaesthesia time (min)	21.7 ± 10.8	21.9 ± 11.9
Recovery time (min)	8.26 ± 4.41	6.95 ± 2.99*
Vol of iso used (mL)	7.0 ± 2.67	–
Vol of sevo used (mL)	–	18.19 ± 3.63

Conclusion: The cost of induction and maintenance of anaesthesia with sevoflurane in patients undergoing day case surgery is similar to propofol and isoflurane.

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PATIENT SAFETY: EQUIPMENT, MONITORING AND COMPUTERS

A.63 Evaluation of respiratory problems during prolonged usage of cuffed oropharyngeal airways. Comparison with laryngeal mask airway

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Aim of the Study: To evaluate objective differences in airway parameters and respiratory side effects between COPA and LMA in patients undergoing prolonged procedures.

Methods: 140 patients, ASA I–III, aged 64 ± 11 years, scheduled for limbs or surface prolonged procedures (>1 h) were randomly assigned to one of two airway management groups (COPA n = 72, LMA, n = 68). Patients with anticipated airway difficulties and those at high risk of regurgitation were excluded. The selection of size and the insertion technique for both airways used were carried out according to the inventors' guidelines. All patients received i.v. propofol 2.0–2.5 mg/kg and fentanyl 1 μg/kg for induction; N_2O 66% in O_2 and sevoflurane 1–4% for maintenance. Ventilation was manually assisted until a regular breathing pattern was established and supplemental doses of fentanyl 25 μg were administered when required. The presence of difficulties in airway insertion, signs of airway obstruction, laryngospasm, regurgitation, desaturation persisting >30 s. (SpO_2 90–94%: +, <90%: ++) and hypercarbia persisting >3 min ($ETCO_2$ 45–52.5 mmHg: +, >52.5 mmHg: ++) were recorded.

Results: There was no difference between the groups in terms of demographic data and length of surgical procedure (COPA: 89 ± 28 min, range: 70–270 min; LMA: 95 ± 37 min, range: 60–410 min). No patient required intensive care management or any additional treatment postoperatively. All results in the table are expressed as probability (%).

Problem	Group COPA		Group LMA		P**
	+	++	+	++	
– Difficult insertion	2.8[a]	0	7.4[a]	0	0.3
	2.8[b]	0	4.4[b]	0	
– Compromised airway	16.7[c]	2.8*[c]	4.4[c]	0	0.08
			2.9[d]		
– Desaturation	5.5	2.8	4.4	2.9	1.0
– Hyrercarbia	38.9	4.1	42.6	1.5	0.7

+: moderate, ++: severe, [a]coughing or gagging, [b]multiple attempts, [c]airway obstruction, [d]laryngospasm, *need for LMA insertion, **chi-square test.

Conclusion: The prolonged use of COPA appears to be an acceptable alternative to LMA in spontaneously breathing patients under general anaesthesia. The incidence of respiratory problems did not differ in both groups.

A.64 Choice of cuff inflation medium during nitrous oxide anaesthesia

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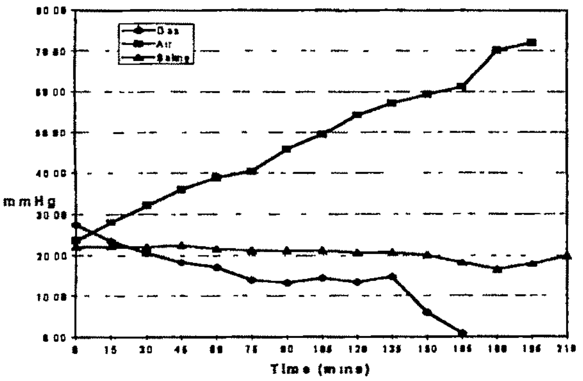
Background & Goal of Study: An increase in tracheal tube cuff pressure is seen during anaesthesia incorporating nitrous oxide if air is used to inflate the cuff [1] It has been suggested that this increase in pressure might cause morbidity and could be avoided by filling the cuff with anaesthetic gas mixture or saline [2, 3] We undertook this study because we had noticed that cuffs inflated with gas mixture sometimes deflated.

Materials & Methods: 30 patients undergoing elective neurosurgical procedures were randomly assigned to one of three groups and following intravenous induction of anaesthesia and neuromuscular paralysis, the trachea was intubated with a reinforced tracheal tube The cuff of the tracheal tube was inflated with either air, sterile 0.9% saline or anaesthetic gas mixture (66% N_2O/33%O_2), the cuff pressure was adjusted to between 18 and 30 mmHg and recorded at 15 minute intervals for the duration of anaesthesia Patients were interviewed the day after the operation to determine the incidence of hoarseness and sore throat Multiple regression analysis was used to test the hypothesis that there is no change in cuff pressure over time

Results & Discussion: Large increases in cuff pressure were seen in the air group, but no morbidity resulted The intra-cuff pressure decreased in the gas mix group and leaks occurred in some patients The pressure remained stable in the saline group. The null hypothesis was rejected in both the gas and air groups

Changes in Tracheal Cuff Pressure
(mean values in each group in mmHg)



Conclusions: The use of gas mix results in deflation of the cuff and cannot be recommended because of the risks of hypoventilation and aspiration Saline provides stable cuff pressures during nitrous oxide anaesthesia but initial adjustment of cuff volume is often required Cuff pressure increases markedly when air is used for cuff inflation, but we found no evidence of any consequent morbidity. Air is therefore the agent of choice in patients at risk of regurgitation

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A.65 Attenuation of vasomotor responses to tracheal intubation. Comparison of tramadol, pethidine, nalbuphine and placebo

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Introduction: Tramadol, an opioid acting primarily at μ-receptors and on the monoaminergic modulating systems, is not habituating or respiratory depressant, but has an efficacy comparable to pethidine and nalbuphine [1, 2]. This study was undertaken to compare the relative abilities of equipotent doses of tramadol, pethidine and nalbuphine to attenuate the vasomotor responses to tracheal intubation

Methods: With informed consent and Ethical Committee approval 280 patients were studied. All received temazepam 0.5 mg kg^{-1} as premedication and randomly received tramadol 3.0 mg kg^{-1}, pethidine 1.5 mg kg^{-1}, nalbuphine 0.3 mg kg^{-1} or isotonic saline 0.02 ml kg^{-1} intravenously (I.V) prior to induction of anaesthesia with thiopentone 4.0 mg kg^{-1}, atracurium 0.6 mg kg^{-1}. Recordings of heart rate (HR), systolic, diastolic and mean arterial pressures (SAP, DAP and MAP) were made prior to injection of test drug, 60 seconds after induction of anaesthesia and at 1, 3, 5, and 7 minutes after laryngoscopy and tracheal intubation Data were analysed by ANOVA and Students' 't' tests, with $p < 0.05$ significant

Results:

		Heart rate (bpm)				SAP (mm Hg)			
		Pre-ind		Peak post-int		Pre-ind		Peak post-int	
	N	M	SD	M	SD	M	SD	M	SD
Sal	69	90	22	117	21	121	20	146	30
Tram	70	93	22	120	23	118	16	142	25
Peth	69	91	22	123	23	119	19	135	28
Nalb	72	89	22	109	18	117	17	130	26

N = patient number, Data given as M (mean) SD

Increases in HR and SAP were maximal 1 minute after intubation, and were significant in each group ($p < 0.001$ each drug and each comparison versus baseline) Tachycardia after nalbuphine was less than after placebo ($p < 0.02$), tramadol ($p < 0.005$) and pethidine ($p < 0.001$) Hypertension after nalbuphine was less than with placebo ($p < 0.001$) and tramadol ($p < 0.01$), but similar to pethidine

Conclusion: Attenuation of the cardiovascular responses to tracheal intubation tests the efficacy and speed of onset of an analgesic Here, tramadol proved indistinguishable from saline (placebo), pethidine reduced the hypertension but induced most tachycardia (reflecting its atropine-like effect), while nalbuphine most effectively reduced all responses to intubation. Since tramadol, pethidine, morphine and nalbuphine have similar analgesic efficacy [1, 2], tramadols inefficacy in this study may reflect a slow onset and suggests it may be better given some 5 minutes prior to intubation [3]

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A.66 Airway management and the incidence of sore throat

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Background and Goals of Study: Since the introduction of the laryngeal mask airway (LMA) in 1983, minor morbidity following its use have been documented but there is a wide variation in the incidence of reported problems[1, 2] This prospective audit was undertaken firstly to establish the pattern of usage of airway devices in elective surgery by consultant anaesthetists and secondly to establish the incidence of sore throat following the use of these devices.

Materials and Methods: 968 consecutive fasted adult patients presenting for general surgical, gynaecological, orthopaedic and genitourinary procedures under general anaesthesia were audited The age, sex, surgical procedure, duration of surgery, airway device used (LMA, tracheal tube (TT), or face mask (FM)) and the use of lubricant were recorded Patients were asked whether they had a sore throat immediately prior to discharge to the ward (early) and again before discharge from hospital (late) Data was analysed using the statistics software package SAS version 6.08

Results and Discussion: Management of the airway was with the LMA in 791 patients (81.7%), the TT in 71 patients (7.3%) and the FM in 106 patients (11%). Logistic regression models fitted to the proportion of patients having a sore throat in the recovery room (early) showed a significant difference between the airway device used in the incidence of sore throat ($p < 0.0001$). The early incidence of sore throat was 27.0%, 14.3% and 1.5% when the airway device used was a TT, LMA or FM respectively. The corresponding late incidence of sore throat was 5.8%, 3.1% and 0%. Age, duration of surgery or lubricant use had no effect on the incidence of sore throat. The overall incidence of sore throat was higher in women (11.4%) than in men (7.5%)

Conclusions: In elective surgery, the 1st choice for airway management with this group of consultants is the LMA, the TT only being used when there is a specific indication. A significant difference was found in the incidence of sore throat between the 3 airway devices.

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A.67

Swallowing after thyroidectomy in patients over 70 years of age without recurrent laryngeal nerve damage

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The aim of this prospective study is to evaluate swallowing difficulties after thyroidectomy in patients over 70 years of age having no recurrent laryngeal nerve (RLN) damage.

Patients and Methods: Patients over 70 years of age (n = 123) who had undergone thyroidectomy under general anaesthesia were divided into two successive groups. In group I (n = 50), patients had a laryngeal examination and a chest x-ray after ingestion of 10 cc of a contrast medium (Hytrast®) before and after surgery at day (D0) then day 2 (D2). Group II patients (n = 73) underwent only the laryngeal examination at D0 and D2. Tracheobronchial aspirations (TBA) were evaluated using nurses' (N) and patients' (P) daily reports. Three supplementary evaluations were performed in group I: ENT evaluation (D2), clinical and x-ray reports after Hytrast® ingestion. The consequences of TBA were determined using chest x-rays and thermal curves.

Results: 10 patients out of 123 (76 ± 5 yrs) having RLN damage were excluded from the analysis. The table shows patients with TBA on N and P reports. In GI, the ENT evaluation showed no TBA, Hytrast® ingestion x-rays showed one clinical and one radiological TBA. X-ray analysis showed ventilation difficulties in one patient with radiological TBA as well as in 6 other without signs of TBA, primarily flat atelectasias. Thermal curve results revealed temperatures above 37.7°C in 1 patient at D0, 11 at D1, 7 at D2 and 3 at D3.

Table: Thyroidectomies: patients over 70 yrs without RLN damage and with tracheobronchial aspiration (TBA)

	N0	P0	N1	P1	N2	P2	N3	P3
TBA (n)	0	4	1	2	0	2	0	2
Patient (n)	91	74	88	79	66	75	42	75
TBA (%)	0	5.4	1.1	2.5	0	2.7	0	1.3

N: nurses reports P: patient reports, 0 = D0; 1 = D1; 2 = D2; 3 = D3

Conclusion: After thyroidectomy, approximately 5% of patients over the age of 70 without RLN damage had TBA's. These TBA disappeared in more than half of these patients at day 3.

A.68

Swallowing after thyroidectomy: impact of recurrent laryngeal nerve damage in patients less than 70 years of age

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The aim of this prospective study is to evaluate swallowing difficulties after thyroidectomy.

Patients and Methods: Patients less than 70 years of age were divided into two groups according to the results of a laryngeal examination performed in the recovery room: GI (n = 100), patients with RLN damage; GII (n = 100), patients without RLN damage, each chosen at random. Each patient underwent a laryngeal exam and a chest x-ray after ingestion of 10 cc of a contrast medium (Hytrast®) prior to surgery and after surgery on day 0 (D0) then day 2 (D2). Tracheobronchial aspirations (TBA) were rated using five different evaluations: nurses' (N) and patients' (P) daily reports, ENT evaluations (D2), clinical reports and x-rays after Hytrast® ingestion. The consequences of TBA were evaluated using x-rays and thermal curves. Statistical analysis included Fischer (2-tail) exact and Mann Whitney tests ($p < 0.05$).

Results: ASA physical status, anaesthesia, surgical technique, pain and side effects were comparable in the two groups. In GII, 3 patients were excluded because of ENT abnormalities detected on D2. The table shows the patients suffering from TBA for N and P. In GI, 10 patients TBA were shown upon ENT evaluation, for the clinical report and x-ray after Hytrast® 3 patients in each group and 1 patient in GI. X-ray analysis showed 14 and 15 patients with ventilation difficulties in GI and GII respectively, primarily flat atelectasias. There was no significant difference between the number of patients with >37.7°C.

Table: Thyroidectomies: patients <70 yrs suffering from tracheobronchial aspirations

	N0	P0	N1	P1	N2	P2	N3	P3
GI (n)	23^{+}	20^{+}	20^{+}	18^{+}	12^{+}	9*	6*	4
GII (n)	1	4	1	1	1	0	0	0

GI: RLN damage (n = 100) N: nurses reports, GII: without RLN damage (n = 97) P: patient reports, 0 = D0; 1 = D1 2 = D2 3 = D3, $^{+}$: $p < 0.01$, *: $p < 0.05$

Conclusion: After thyroid surgery, RLN damage is associated with 20% TBA ($p < 0.01$). These TBA are rarely shown by Hytrast®. They disappear in 50% and 75% of patients at D2 and D3 respectively. In this series, the radiographic and thermal consequences are not significant.

A.69

Effects of endotracheal intubation and laryngeal mask airway insertion on the risk of myocardial ischaemia in cardiac patients

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Background & Goal of Study: The aim of this sudy was to compare the effects of endotracheal intubation (ET) and insertion of laryngeal mask airway (LMA) to the risk of myocardial ischemia in patients with coronary artery disease (CAD) during non-cardiac surgery.

Materials & Methods: After Faculty Ethics Committee approval and patients' written consent 30 patients, 60–80 years old, ASA III–IV scheduled for elective peripheric surgery were included in the study. Patients were evaluated by Goldman and Detsky Cardiac Risk Index and according to the results of echocardiography before surgery then were assigned into two groups (n = 15) equally according to the risk factors. Anaesthesia was induced with 0.2 mg/kg etomidate, 15 μg/kg alfentanil, 0.1 mg/kg vecuronium bromide i.v. in all patients. In the I. group the patients were intubated, in the II. group LMA was inserted for maintenance of airway. Mean arterial pressure (MAP), heart rate (HR), rate-pressure product (RPP) and ST segment changes with 5 lead ECG were recorded before and after induction, during and after 1, 3, 5 minutes of airway manipulation. 12 Lead ECG and CPK, CPKMB levels were recorded preoperatively and 6., 24. hours postoperatively. The results were compared statistically with ANOVA, Tukey Kramer, Student Keuls and Fischer's Exact tests ($p < 0.05$).

Results & Discussion: MAP, HR and RPP increased significantly 1 minute after intubation in the I. group, there was no difference in MAP and RPP and a significant decrease in HR at all time intervals in the II. group. ST segment changes were recorded 15 times in 6 patients in the I. group and 4 times in 3 patients in LMA group ($p < 0.05$). CPKMB value was greater than 25 IU/ml in 3 patients who had ST segment changes in the I. group.

Conclusion: Unless contraindicated; airway maintenance by LMA causing less hemodynamic and ST segment changes compared to ET should be preferred in patients with CAD in order to protect myocardial perfusion.

A.70

Use of a cuffed oropharyngeal airway to assist fibreoptic laryngoscopy and tracheal intubation using the Portex bougie

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Background: The Cuffed Oro-Pharyngeal Airway (COPA) is a new device based on a Guedel airway, but with a pharyngeal cuff and a standard 15 mm connector. Its internal dimensions allow a fibreoptic laryngoscope (FOL) to pass through it. A new bougie is now marketed. It has a Coudé tip, is hollow, disposable and cheaper to produce than the gum elastic bougie. It also fits through the COPA, so may be of use with a FOL when conventional methods for tracheal intubation prove difficult.

Goal: To evaluate the COPA in assisting fibreoptic tracheal intubation with the bougie.

Methods: 20 adult patients, ASA 1–2, were recruited. Those at risk of reflux or difficulty with intubation were excluded. They were anaesthetised and paralysed. After 3 minutes, direct laryngoscopy was performed. A COPA was then inserted and manual ventilatory support continued. The FOL was passed through the COPA via a sealed angle piece. The laryngeal view was scored thus: 4, only cords seen; 3, cords plus posterior epiglottis; 2, cords plus anterior epiglottis; 1, cords not seen (1). Manipulations needed to improve the view were noted. The bougie was passed through the COPA and attempts made to advance it into the trachea. If successful, the FOL and COPA were removed and an endotracheal tube (ETT) railroaded over the bougie. The time from FOL insertion to intubation of the trachea was recorded. 2 anaesthetists performed all manoeuvres for 10 cases each.

Results and Discussion: Ventilation was satisfactory in all cases, needing increased fresh gas flow in 4 to overcome a leak. In 12/20 there was some view of the larynx after insertion of the COPA (a score of 2, 3 or 4) increasing to 19 after manipulations which included; jaw lift, downward rotation of COPA, slight pulling out of COPA. Intubation was easy in 11/20 with 5 causing slight difficulty and 4 being very difficult. The Coudé tip impinging on the anterior larynx caused most difficulties. This was overcome by rotating the bougie in 5 cases and removing it to use its opposite end in 4. The mean times for intubation for the anaesthetists were 124 and 127 seconds (no significant difference). There was a tendency toward a learning curve but no plateau was reached. This contrasts with a study using the Aintree catheter (a ventilation/exchange catheter) on the FOL (2) instead of a bougie. This showed faster intubation times; less difficulty with intubation and no learning curve. Overall, the COPA is easy to use and one can intubate through it though a bougie is not the ideal tool to use

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A.71 Optimum cuff inflation in cuffed oropharyngeal airway

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Background: COPA is a new airway recommended for short-term procedures involving spontaneously breathing patients with little risk of aspiration. When the COPA is inserted it is necessary to produce a seal so that adequate minute volumes may be achieved, for the period that the patient is manually ventilated, to the time of spontaneous ventilation restoration. Previous experience with cuffed airways has shown that overinflation produces a marked increase in pressure applied to the mucosal wall resulting in mucosal ischaemia (1). Although certain volumes of air have been suggested as appropriate for the different COPA sizes, the justification for these has not been established with respect to the pressures applied to the pharyngeal mucosa. This study investigates the optimum cuff inflation in order to achieve a seal for adequate minute ventilation.

Materials and Methods: In the study were included 22 fasted patients (ASA I–II). Anaesthesia was induced with propofol 2–2.5 mg/kg and fentanyl 1 $\mu g/kg$ and maintained with N_2O 66% in O_2 and sevoflurane 2%. After induction the COPA (sizes 9, 10) was inserted and the cuff inflated with air 30 ml and 35 ml respectively (Vcuff initial), according to manufacturer instructions and the cuff pressure measured by a connection to a standard pressure transducer (Pcuff initial). Then the patient was mannually ventilated and checked for a leak sound from the cuff. The cuff was then deflated or inflated appropriately in order to achieve a seal at a peak airway pressure of 17 cmH_2O. The final cuff volumes and cuff pressures as well as the tidal volumes (V_T) achieved were recorded.

Results: Cuff was deflated in 14 patients (63.6%), inflated in 6 (27.3%) while no adjustment was needed in 2 (9.1%). Our results are summarized in the table:

	V cuff (ml)	Pcuff (cmH_2O)	V_T (ml)
Initial	32 ± 3	100 ± 29	882 ± 206
Final	29 ± 6	71 ± 39	837 ± 169
P-value	0.02	0.008	0.4 (NS)

Conclusion: Our results demonstrate that the manufacturer's suggested cuff volumes do not necessarily fit to all patients and so there is a need of further titration in order to achieve a seal that is a prerequisite for a safe and effective ventilation

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A.72 Clinical evaluation of the cuffed oropharyngeal airway during positive-pressure ventilation

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Background: The utility of the Cuffed Oropharyngeal Airway (COPA) during positive-pressure ventilation has yet to be determined. The aim of this study was to evaluate the utility of the COPA during positive-pressure ventilation and to assess whether significant leaks occurred and if leaks were associated with gastroesophageal insufflation.

Methods: 75 patients (ASA I–III, 60 male, 15 female) undergoing elective urologic surgery received a standard anesthetic technique of alfentanil 12.7 ± 3.7 $\mu g/kg$ followed by propofol 2.7 ± 0.5 mg/kg for induction and O_2/N_2O/propofol for maintenance. After induction of anesthesia and insertion of the COPA controlled ventilation was used with four different peak pressure settings (10, 15, 20 and 25 cmH_2O) in each patient. Data collected included the ease of insertion and quality of "hands-free" anesthesia, inspiratory and expiratory volumes, gastroesophageal insufflation and leak at the neck

Results: Average duration of COPA ventilation was 54 min (range 20–150 min.). Insertion of the device was easy in 73 cases (98%). In 51 patients (68%) additional manipulations (e.g. changing of COPA size, increasing cuff volume, hyperextension or turning of the head) were necessary to reach satisfactory ventilation. The overall rating of the COPA was noted as excellent in 42 cases (56%), good in 17 cases (23%), fair in 11 cases (15%) and poor in 5 cases (7%). In 2 patients (3%) endotracheal intubation became necessary because of inadequate airway seal and patient bucking. No severe side effects like laryngospasm, regurgitation, aspiration or teeth damage were registered. One patient developed a sore throat. Blood tinged secretion was noted in 3 cases.

Tidal volumes (mean ± SD) at 10, 15, 20 and 25 cmH_2O were 510 ± 158 ml, 726 ± 201 ml, 863 ± 226 ml and 996 ± 235 ml, respectively. Leak fractions at these pressure settings were 0.09 ± 0.08, 0.12 ± 0.12, 0.16 ± 0.14 and 0.16 ± 0.12, respectively. The frequency of gastric insufflation ranged from 1.3% at a ventilation pressure of 10 cmH_2O to 12.5% at 25 cmH_2O. The mean peak pressure to reach a tidal volume of 10 ml/kg was 18.5 cmH_2O (range 11–30 cmH_2O). Gastric insufflation occurred in 4%

Conclusion: The COPA provides adequate positive-pressure ventilation during general anesthesia for interventions of limited duration. The handling of the COPA is easy and the device is well tolerated. It is contra-indicated in patients with increased risk for aspiration

As gastroesophagal insufflation of air becomes a problem in the presence of increased ventilation pressures, airway resistance and compliance must be satisfactory.

A.73 A comparison of the laryngeal mask airway and the cuffed oropharyngeal airway for manual positive pressure ventilation

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Background and Goal of Study: The internal diameter and length of the laryngeal mask airway (LMA) are optimum as regards the airway resistance, but the flexible bars in the bowl of the LMA may impede gas flow (1). The cuffed oropharyngeal airway (COPA) is a new form of airway which performs as a non-invasive aid in airway management recommended for short-term procedures involving spontaneously breathing patients with little risk of aspiration. In this comparative study we investigated the possible differences between the most commonly used LMA sizes (3 and 4) and COPA (length 10 cm) concerning the ventilatory variables during manual positive pressure ventilation (MPPV)

Methods: After institutional approval and written informed consent 30 ASA I–II adult patients scheduled for procedures under general anaesthesia with spontaneous ventilation underwent a double comparative trial. Patients with anticipated airway difficulties and those at high risk of regurgitation were excluded. General anaesthesia was induced with midazolam 0.04 mg/kg, fentanyl 2 $\mu g/kg$ and propofol 2.5 mg/kg and was maintained with sevoflurane 1–4% and N_2O 66% in O_2. All patients initially underwent gentle MPPV with COPA for three minutes. The maximum values of tidal volume (V_T) and the peak inspiratory pressure in which air-leak occurred (Paw-leak) were recorded. Afterwards the COPA was replaced by LMA and the same ventilatory variables were recorded. All measurements were made during the post-induction apnoeic period with the patient in supine position and before skin incision

Results: Are summarized in the table

	COPA	LMA	P-value
Paw-leak (cm H2O)	18.4 ± 3.8	26.3 ± 4.7	<0.0001
V_T (ml/kg)	12.2 ± 3.0	13.8 ± 4.3	0.1

Conclusion: LMA provides a better airway seal that contributes in achievement of higher values of Paw-leak, although MPPV through the COPA seems to offer similar VTs. However, our measurements and results apparently concern a healthy surgical population

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A.74 Comparison of cuffed oropharyngeal airway and laryngeal mask airway

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Background and Goal of the Study: The COPA[1] is a modified Guedel airway device with a specially designed cuff at its distal end and a 15 mm connector at its proximal end. It was the aim of the study to compare the COPA with the LMA[2] on 1) haemodynamic (blood pressure and heart rate) and cerebral responses (changes in bispectral index) at insertion of the device, 2) quality of insertion and maintenance of a free airway, 3) need for additional manipulations, 4) side effects and 5) complications.

Methods and Material: After institutional approval and patient consent, 35 female patients (18 COPA and 17 LMA) scheduled for short ambulatory gynaecological procedures were included. Patients were premedicated with midazolam (0.03 mg/kg 5 min and alfentanil 0.5 mg 2 min before induction. Anaesthesia was induced and maintained with a propofol target controlled infusion device (Stanpump®). The COPA/LMA was inserted 4 min after induction. Spontaneous breathing was aimed at. Data are presented as mean ± SD. Data were analysed using ANOVA and t-test for paired data.

Results and Discussion: Anthropometric data were similar in both groups. At insertion, more pronounced increase in diastolic blood pressure

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was found in LMA ($p < 0.05$). Increase in systolic blood pressure and heart rate was similar in both groups. Cerebral response, defined as bispectral index increase, was for LMA 12 ± 10 and for COPA 15 ± 10 (NS). Quality of insertion was easy For the LMA 100% at the first attempt and for the COPA 89% at first and 11% at second attempt No failure was observed. Airway support during insertion and maintenance was better in the LMA group, more additional manipulations (jaw thrust, hyperextension or both) were necessary in the COPA group. No additional manipulations were necessary in LMA. Quality of inflation and deflation of the cuff and removal of the device was nearly identical in both groups. Side effects were few in both groups (coughing 2/17 LMA vs. 1/18 COPA; bucking 2/17 LMA vs. 0/18 COPA; blood on the cuff (3/17) and lip trauma (1/17) in LMA vs blood on the cuff (3/18) COPA). No laryngospasm nor regurgitation were seen in both groups.

Conclusions: No differences in haemodynamic and cerebral stimulation was observed during the insertion of both devices Compared to the LMA, the insertion of the COPA is easier but needs more additional manipulations to obtain adequate airway support. The COPA is a single use device with an excellent overall quality for airway support in sponteneously breathing patients.

Acknowledgement: COPA devices were provided generously by Mallinckrodt Medical INC

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A.75 Use of esmolol to attenuate haemodynamic responses to tracheal intubation, eye bandaging and tracheal extubation during cataract surgery

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Introduction: Esmolol attenuates haemodynamic responses to intubation and extubation [1, 2]. At the end of cataract surgery, gentamycin injection and eye bandaging have chronotropic and inotropic effects, augmented by reversal of neuromuscular blockade (RNB) and extubation [3] We investigated the effects of 1) esmolol 4 0 $mg.kg^{-1}$ given IV 90 secs prior to intubation and 2) esmolol 2.0 $mg.kg^{-1}$ given 60 secs prior to each of gentamycin injection and extubation.

Method: With Ethics Committee approval and patient consent 80 mature age patients were randomised to receive esmolol (E) or placebo (P) Anaesthesia was standardised. Pre-induction HR/SAP was compared with maximum changes after 1) induction and 2) tracheal extubation, end-surgery HR/SAP was compared with maximum changes after 1) eye bandaging, 2) RNB and 3) extubation. Analyses used ANOVA, Chi^2 and 't' tests ($p < 0.05$ significance).

Results: With placebo, HR increased after intubation ($p < 0.001$), RNB ($p < 0.001$) and extubation ($p < 0.001$); SAP fell after induction ($p < 0.01$), increased after intubation ($p < 0.001$), RNB ($p < 0.005$) and extubation ($p < 0.001$) With esmolol, HR decreased after induction ($p < 0.05$) was unaffected by intubation, bandaging and extubation; SAP fell after induction ($p < 0.001$), normalised after intubation, bandaging and RNB, but fell after extubation ($p < 0.001$)

	Pre indu	Post indu	Post intbn	End surg	Post band	Post RNB	Post extbn
P HR	73	79	96	66	71	84	94
SAP	153	127	178	123	141	150	165
E HR	77	69	75	69	65	77	76
SAP	162	117	149	126	127	135	116

* = significant change v preceding baseline. Data = mean value

Conclusion: Esmolol given 60 to 90 secs before these noxious stimuli attenuated rises in HR and SAP, but caused transient hypotension before or after the stimulus. This data suggests that repeat esmolol injection before extubation is unnecessary, and that, in view of the rapid onset of action of esmolol, the timing of esmolol injection in relation to these noxious stimuli needs studying

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A.76 Intubation without muscle relaxants in Mallampati grade III and IV patients with mandibular fracture

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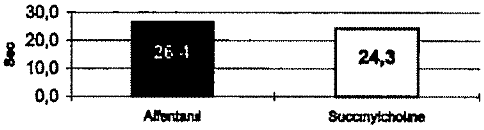
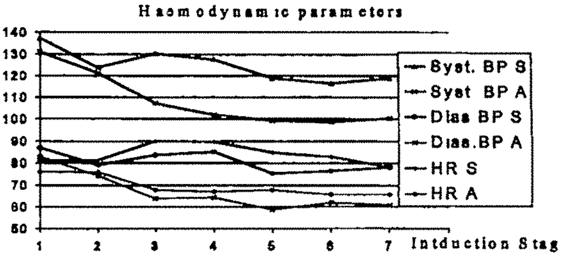
Background and Goal of Study: Intubation without muscle relaxants (MR) gains more and more wider acceptance but there is still a lot of controversy for what types of patients it is suitable. Patients with mandibular fractures are presenting with Mallampati III and IV grades, caused mostly by pain The local survey showed them to be considered by anaesthesiologists as not suitable for induction without use of MR The present study aims to address this issue.

Materials and Methods: After obtaining Ethics Committee approval 52 patients (ASA I/II) were randomly allocated to two groups 26 patients each Patients received propofol 2 mg/kg and alfentanil 0.5 mg/kg for induction, in I group, and propofol 2 mg/kg and succinylcholine 1.5 mg/kg in II, and were intubated via nasal route. The same pre-induction routine was used in both groups. The laryngoscope grade, ease and duration of intubation, and haemodynamic (HD) parameters such as BP, HR, and Sat O_2 were assessed.

Results and Discussion: In both groups intubation was regarded as easy by performing anaesthesiologists The mean time to perform intubation, was 26 4 sec in alfentanil and 24.3 sec in succinylcholine group.



The mean laryngoscope grade was 1.7 and 1.3 respectfully. The HD parameters and oxygenation were evaluated.



Sat O_2 was maintained between 98% and 99% in both groups

Conclusions: Intubation without MR is possible in the group of patients with mandibular fracure and can be perform as easily and quickly as with MR which gives us useful alternative for induction of anaesthesia in this patient group. *Anaesthesia*, **general***Intubation, tracheal, nasal**Drugs,* **propofol, alfentanil, succinylcholine**

A.77 Safety and simplicity of difficult tracheal intubation management: comparison of the Bullard laryngoscope with the video-optical intubation stylet in a mannequin

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Background and Goal of the Study: The Bullard laryngoscope (BL) has been reported as a valuable aid in the management of the unpredicted difficult tracheal intubation.[1] The video-optical intubation stylet (VOIS) is a new indirect laryngoscopic intubation device, designed for the management of difficult direct laryngoscopy.[2] It transmits the view from the endotracheal tube (ETT) tip to a video display. This allows the anaesthetist during difficult intubation to guide the ETT into the trachea under visual control. The purpose of this study was to ascertain, if the VOIS is safer and easier to master than the BL

Material and Methods: A mannequin has been adjusted so that only the tip of the epiglottis was just visible using a Macintosh blade (grade III view) 40 anaesthetists of different years of experience were asked to attempt tracheal intubation using the BL and the VOIS One demonstration was followed by one practical attempt. Then each anaesthetist performed each technique 10 times in succession (order randomized). Time was recorded of each attempt. Failed intubations were defined as those, which required more than 60 s or which resulted in esophageal intubations At the end of each sequence the anaesthetists were asked to attach a degree of difficulty using a scale from 1 (extremely easy) to 5 (impossible) The results were statistically evaluated using Mann-Whithey-U-test and Pearson-Chi-square-test

Results:

	Bullard	VOIS	p
Successful intubations	359/400	392/400	0 003
Failed intubations	41	8	0.003
Oesophageal intubations	21	1	0 003
Intubation time (s)	19.2 ± 4 5	18 8 ± 4 6	ns
Degree of Difficulty	2 63	1 68	0.0001

Discussion and Conclusions: Because of fewer failed intubations and a lower degree of difficulty, management of difficult tracheal intubation seems to be safer and easier with the video-optical intubation stylet, than with the Bullard laryngoscope. Our results suggest, that VOIS could become a valuable aid for unpredicted difficult intubations with very little training.

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A.78 Evaluation of McCoy laryngoscope in routine laryngoscopy

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Introduction: The use of the Mc Coy levering laryngoscope is associated with significantly less force required during laryngoscopy. The purpose of this study was to investigate whether the tip elevation results in better laryngeal visualisation during routine laryngoscopy.

Methods: During six months, 300 adult patients, undergoing elective surgery, were investigated in a prospective and descriptive study. The patent upper airway was appreciated with preoperative assesment tests. body mass index, mouth opening, Mallampati classification, neck movement and thyro-mental distance Patients with a known difficult intubation, with risk of regurgitation and with airway assesment test of impossible intubation were not included. All laryngoscopies were performed by nine confirmed anaesthetists with experience in the use of Mc Coy laryngoscope. Each anesthesia was standardised with lidocaine IV (1.5 $mg.kg^{-1}$) and propofol (5 $mg.kg^{-1}$). Head and neck were positioned in the "sniffing" position. The Mc Coy blade (size 3 or 4) was used and the laryngeal view was evalued with Cormack score, in five successive situations. The two first without levering tip as an ordinary Macintosh blade: S1 with usual forwards and upwards elevation of the oro-pharyngeal structures and S2 with elevation and anterior laryngeal pressure. The three next with levering tip: S3 without and S4 with usual elevation, S5 with elevation and anterior laryngeal pressure. The results of Cormack score were colliged in each situations ANOVA including repeated measures was applied to compare the results between different situations.

Results: ANOVA showed statistical significant differences between S5 and the others situations ($p < 0.001$)

	Without tip elevation		with tip elevation		
	S1	S2	S3	S4	S5
Grade I	62	193	14	110	257
Grade II	144	91	128	154	42
Grade III	90	16	145	36	1
Grade IV	4	0	13	0	0

S1 vs S3 $p < 0 001$, S2 vs S4 $p < 0 001$, S2 vs S5 $p < 0 001$

Discussion: Without any applied forces on the handle to expose glottic aperture, levering tip is not sufficient to see correctly vocal cords (S3) In clinical practice with a standardised intubation condition, use of the activated Mc Coy blade with additional manoeuvres as ALP (S5) gave best laryngeal views

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A.79 Difficult airway management in cardiac anaesthesia: the role of transillumination guided intubation

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Background and Goal: As a result of further development of the intubation device (Trachlight®, Laerdale), the transillumination guided intubation (TGI) presents itself as an alternative to the direct laryngoscopic intubation [1] Especially cardiosurgical patients require a hemodynamically stable induction, also under complex laryngoscopy. Does the TGI with the Trachlight® present itself as an assistance especially in regards to difficult laryngoscopy conditions?

Methods: Cardiosurgical patients (NYHA III and IV) were induced with Etomidate, Midazolam, Sufentanil and Pancuronium. After the first futile intubation attempt by means of direct laryngoscopy (with non-adjustable vocal cord level) application of the Trachlight® for TGI performed by an experienced specialist Recorded parameters: success, duration, blood pressure, heart rate.

Results: Out of 1034 patients (June–November 1997) 22 patients which could not be directly intubated by laryngoscopy (vocal cord level and arytenoid cartilage not visible, were a part of the study. In 18 cases (82%), the light guided intubation was successful as secondary procedure. In 4 cases, after failure of the TGI, the direct laryngoscopic intubation was performed after 2 attempts in each case. The directly measured arterial blood pressure elevated by 15% in comparison with the pressure prior to the passage through the larynx, the heart rate did not change. In 10 cases, the duration was less than 30 s, in 8 cases 30–60 s

Discussion and Conclusions: After sufficient familiarization of 2 specialists with the technique of the TGI, the TGI was introduced as an alternative in case of difficult intubation because of the positive experience [2]. The lack of transillumination effect with adipose patients could be adjusted by dimming of the induction room. The method does not replace the absolutely safe command of the conventional direct laryngoscopy, as indicated by the 4 failures. The smooth and successful outcome in 82% of the cases disclosed however, that the transillumination guided intubation was a rapid uncomplicated assistance in case of difficult intubation conditions

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A.80 The double lumen tube. Indications, application, monitoring (A video film)

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This video aims at inducing familiarity with an important anaesthetic tool· In 1949 E. Carlens for the first time used a double lumen tube (DLT) to prevent the intraoperative spread of tuberculous secretions from the affected into the healthy lung. Absolute indications for airway separation are haemoptysis, bronchiectasis and tracheobronchial fistula, while relative indications all refer to optimizing surgical conditions This traditional distinction no longer is justified considering the surgical precision required, the importance of endoscopic thoracic surgery and the improvement in design and material of DLT's

In this video film the modern polyvinyl right and left-sided DLT's are described in detail, also the correct course of their insertion is exemplified by endoscopic visualization. Clinical checks by auscultation and inspection of DLT-position frequently prove unreliable, as in 15% of our own cases Often primary misplacement into the wrong main bronchus, too far outside or too far down the correct main bronchus cannot be detected clinically By fibreoptic bronchoscopy (FOB), however, a correct position can be verified, malpositions identified and thus corrected immediately. Videobronchoscopic takes from bronchiectases and bronchial sleeve resections serve to demonstrate the importance of the availability of fiberoptic bronchoscopic control of the double lumen tube, since only DLT's offer every option of conventional and differential management of one-lung ventilation, as CPAP or High Frequency Jet Ventilation to the non-dependent, operative lung. Sequences of clinical examples, endoscopic views and computer animations demonstrate how to combine DLT's and FOB into a safe and reliable system for the management of ventilation in non-cardiac thoracic surgery.

A.81 Intubatin laryngeal mask airway (Fastrach®): the learning curve of its use

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Background and Goal of Study: Laryngeal Mask Airway (LMA) has been widely used as an alternative way to ensure airway patency during anaesthesia and resuscitation. The insertion of a LMA is a skill that is easily taught even to inexperienced operators [1] A new modification of the LMA, the Intubating Laryngeal Mask (ILM) Fastrac®, has been developed. It is consisted of a handle, a rigid anatomically curved airway and an epiglottic elevator through which blind endotracheal intubation can be performed. The goal of this study was the assessment of the initial experience of ILM and the documentation of the learning curve of its use.

Materials and Methods: 60 patients scheduled for surgery, Mallampati class I–III, were selected for ILM insertion and subsequent blind endotracheal intubation by two anaesthetists with a wide experience in LMA and with experience only in training manikins in ILM. After the induction of anaesthesia with propofol, insertion of an ILM size 3, 4 or 5 according to the patient weight was attempted When adequate ventilation was established, an endotracheal armoured tube 30–32 Fr was blindly inserted through the ILM. Throughout the procedure a) the number of attempts required for successful ILM placement b) the success rate of blind endotracheal intubation through the ILM c) details that facilitated the insertion technique d) the time required for the procedure were recorded and documented. After the collection of the data, we drew the learning curve of ILM use for both the anaesthetists.

Results and Discussion: 34 male and 26 female were studied. ILM insertion and adequate ventilation was possible at the first attempt in 53 and second attempt in 7 patients. Blind endotracheal intubation was achieved in 49 patients (after 1 atttempt in 41 and after 2 attempts in 8), and failed in 11 patients The entire procedure lasted 45–90 sec Failed intubations were due to errors of the technique, misplacement of the ILM and, as it was presented by the learning curves, to lack of experience because all the failures were associated with the first patients of the study

Conclusion: The new ILM is very easily inserted in patients. The blind endotracheal intubation through the ILM is a more difficult skill in which success rate is being improved by experience.

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A.82 How to choose the adequate size of a left-sided double-lumen endobronchial tube. An assessment of the radiographic Brodsky's method

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Introduction: Brodsky and al (1) showed that adequate DLT' size can be successfully selected from measurement of the tracheal width on a preoperative posterio-anterior chest radiograph However, we believe that determination of adequate DLT' size must include the followings· difficulties in insertion (DI), fiberoptic bronchoscopic control of adequate catheterization of left main bronchus (FOB), adapted impervious bronchial cuff volume (BCV) and no postoperative tracheal injury (POTI). The aim of our study was therefore to assess the Brodsky and al's method, taking into account the above criteria

Materials and Method: 47 consecutive patients included for planed thoracic surgical procedures with one-lung ventilation were intubated under general anaesthesia with polyvinyl chloride DLT. The choice of the DLT'size was based on radiographic front tracheal width (RTW) according to Brodsky and al (1): 41 French (Fr) when RTW ≥ 18 mm, 39 Fr when RTW ≥ 16 mm, 37 Fr when RTW ≥ 15 mm. Adequate DLT's position was controlled with fiberoptic bronchoscopy. Impervious bronchial cuff volumes were adapted to obtain both a bronchial cuff pressure ≤30 cm H2O and no ventilatory leak. In addition, difficulties in DLT's insertion (passing through glottis, advancing down the trachea), postoperative endotracheal injury (laryngitis or tracheitis needing treatment, sore throat) were noted.

Results: Sex ratio (M/F) was 33/14 All patients were successfully intubated with predicted DLT'size. Adequate lung deflation was obtained in every case No ventilatory leak was noted. Other results are shown on the table. no statistical difference linked to DLT'size was observed.

DLT'size (french)	n (M/F)	DI (%)	FOB (%)	BCV (ml ± SD)	POTI (%)
41	36 (30/6)	26	100	1 7 ± 0 5	27
39 ± 37	11 (3/8)	9	100	1 7 ± 0 6	18

Discussion-Conclusion: It is confirmed that the adequate DLT'size can be selected on the basis of radiographic data; since all patients were successfully intubated with predicted DLT'size with adequate placement and impervious bronchial cuff volume for cuff pressure ≤30 cm d'H2O. Moreover, neither difficulties in insertion nor tracheal injuries depended on DLT'size. Postoperative injuries were limited to temporary sore throat.

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A.83 A new modality of high-frequency ventilation: superposition of two jet streams

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Background and Goal of Study: High-frequency jet-ventilation techniques have been introduced as alternative ventilatory modalities during laryngeal and pulmonary surgery and to improve impaired oxygenation (1). However, small tidal volumes delivered at high respiratory rates result in increased levels of arterial CO_2. Therefore, we combined two seperate jet-streams (superposition) with different rates via a special T-connector, enabling normal CO_2 elimination

Materials and Methods: In the perioperative course 33 surgical patients (40 ± 18 yrs) with normal pulmonary function were ventilated with an electronic prototype high-frequency jet-ventilator (Alexander I, Reiner, Austria). Patients were submitted to superimposed high-frequency jet-ventilation (SHFJV) with respirator settings comparable with the preceeding conventional mechanical ventilation (identical FiO_2 and airway pressures) To increase tidal volume a low-frequency (8–14/min) jet-stream and a high-frequency (600/min) jet-stream were applied simultaneously via a special jet-adapter connected to the conventional endotracheal tube. For gas entrainment due to the Venturi effect a bias flow of 15 L/min of humidified and warmed gas was lead through the cross part of the jet-adapter. Data of blood gas analysis (paO_2, $paCO_2$), heart rate (HR) and mean arterial pressure (MAP) during conventional ventilation (CPPV) and after one hour of subsequent SHFJV were compared Data (mean ± SD) were analyzed using the paired *t*-test ($p < 0\ 01$)

Results: SHFJV resulted in increased levels of paO_2 (121 ± 34 *vs* 145 ± 44 mmHg) and decreased values of $paCO_2$ (40 ± 5 *vs* 32 ± 6) HR (77 ± 25 *vs* 75 ± 26) and MAP (69 ± 12 *vs* 72 ± 12) did not change after transition of ventilation to SHFJV.

Conclusion: SHFJV is safe and effective to improve oxygenation. In contrast to solitary HF jet-, SHFJV also facilitates adequate CO_2 elimination by addition of a low-frequent jet-stream, which increases tidal volume. Therefore, benefits of HF jet-ventilation can be utilized in patients over longer periods maintaining normal CO_2 levels

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A.84 A new prototype of an electronic jet ventilator and its humidification system

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Background & Goal of Study: This study introduces a new prototype of an electronic jet-ventilator named ALEXANDER 1, which is capable of simultaneously delivering two separate jet streams with different frequencies to the patient This ventilation technique is called superimposed high-frequency jet-ventilation (SHFJV) We want to show, that the problems of humidification under SHFJV can be prevented using this new jet-ventilator

Material & Methods: Forty patients, 16 female, 24 male with a median age of 67 years (range 55 to 79 years) were randomly allocated to one of four groups (A, B, C, D) ten in each group, receiving either SHFJV by the ALEXANDER 1 (group A and group B), or high frequency oscillation (HFO) by a VDR 4 (group C), or conventional mechanical ventilation (CMV) by an Evita (group D). All patients were ventilated for more than 100 hours because of respiratory insufficiency.[1]

Measurements of the relative humidity (RH) of the inspiration gas (FM-Cl, E u. E. Elektronik Corp , Unterwiesen, Austria) and measurements of the temperature of the inspiration gas were performed (temperature sensor line 21076 A, Hewlett Packard, Palo Alto, CA) twice a day Bronchoscopy (Olympus BF Type 20D, Olympus Optical Co , LTD, Shirikawa, Japan) was performed twice a day too. Humidification and warming of the ventilation gas was done using three different humidification systems In group A, we used a combined form of a humidification and warming-system Whereas the entrained gas (bias flow) was humidified by a hot water humidifier (Aquapor, Type 8406640, Fa. Drager, Corp., Lübeck, Germany), humidification of the jet gas was achieved by a continous infusion of 0.9% saline via a special jet adapter into the high pressure jet line The instilled saline infusion was warmed by a fluid warmer (HL-90 INT, Level 1 Technologies Corp., Rockland, MA, USA) up to 37°C before it reached the jet gas In group B, we used the same system without the fluid warmer. In group C and D, we used a hot water humidifier In all four groups, several patients were exposed to intermittent prone position in case of extremely severe respiratory distress syndrome.

Results & Discussion: To evaluate the amount of tracheobronchial mucosal injury, a scoring system was used, taking into account the size of the area and the extent of macroscopic epithelial damage. Group A, C and D had a mucosal injury score of zero. No significant pathologic evidence could be seen The temperature values (group A: 31.4°C; group C: 32 1°C; group D 34.2°C) were insignificantly different In group B, the temperature was significantly lower (27°C) than in all the other groups. Inflammation of the tracheal mucosa was found and the mucosal injury score was significantly higher.

Conclusion: Using the ALEXANDER 1 for SHFJV with high humidity almost all the problems, which are associated to this ventilation technique, like tracheal and epithelial inflammation, necrotizing tracheobronchitis (NT), etc can be prevented

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A.85 Carbon dioxide absorption without strong alkali

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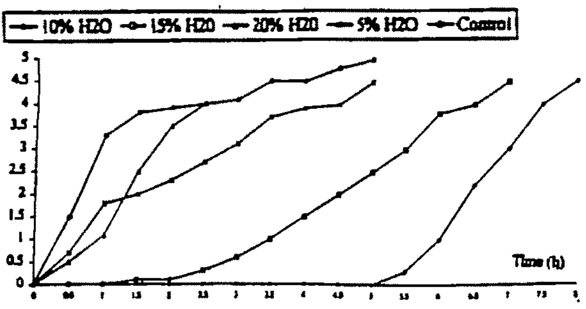
Background and Goal of Study: The interaction between carbon dioxide absorbents containing strong alkali (sodium or barium hydroxide) and volatile anaesthetic agents has recently given cause for concern (1, 2) It has previously been suggested that strong alkali is not required for efficient absorption but that the moisture content of the absorbent is most important (3).

Materials and Methods: Using mixtures of calcium hydroxide and hydrated calcium chloride ($CaCl_2$ $6H_2O$) we produced material with 0%, 5%, 10%, 15% and 20% water content. One hundred grams of the material was placed in a canister and oxygen at 1 l/min with carbon dioxide at 40 ml/min was passed through the material A Datex Capnomac gas analyser was placed at the exit port of the canister and readings were collected directly by a portable computer.

Results: The results are shown as time (hour) against carbon dioxide (kPa).



Conclusion: The water content of a carbon dioxide absorbent is directly related to its ability to absorb CO_2 and strong alkali is not necessarily required.

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A.86 Carbon monoxide production in rebreathing circuits: the halogenated concentration effect

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Introduction: The carbon monoxide (CO) production in the rebreating circuits happens when certain halogenated agents reacts with dryness soda lime (hydrate level lower than 2%) However the mainly factors that determine the severity of CO intoxication during the clinical use of a rebreathing circuit have not been studied, one of these factors can be the minute volume

Objective: To determine carboxyhemoglobin (HbCO) and CO levels (in the rebreathing circuit) using desflurane a differents concentrations.

Material and Methods: Six Large-White swine (weight. 36 ± 3 kg) are anesthetized using desflurane at different concentrations (3 5% and 7%). The dried Soda-Lime is gotten carring across the Soda-Lime canister a oxygen flow during 65 h, obtaining hydrated Soda-Lime level = 1% The anaesthesia machine used was an Elsa-engstrom with the Soda-Lime canister in the inspiratory branch and the halogenated agent was isofluorane.

The experimental sequence is the following

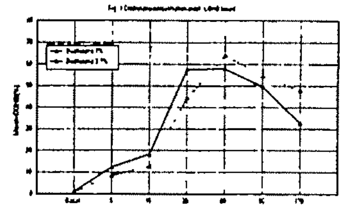
(1) Anesthetic induction and beginning of the mechanical ventilation – fresh gas flow = 8 liters (O2-N2O = 50%), VT = 15 ml/kg and FR = 15-.

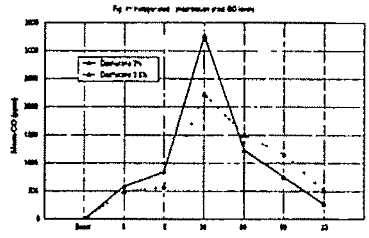
(2) Anesthetic intravenous maintenance and monitoring: TA, PAP, SvO2, ETCO2, sPO2 and T^a.

(3) Change normal hydrated Soda-Lime canister (15%) for dried Soda-lime canister (1%) and opening the desflurane vaporizer to reach an Inspired same us to espired concentration = 7% or 3.5% to the 15 minutes and maintaining these concentrations during the rest of the experience

(4) To the 15 minutes lowered the gas fresh flows to a sixth part of the minute volume until the end of the experience.

We register haemodynamic monitoring data, blood gas measurements and we analyzed the HbCO and the CO (in the Inspiratory branch) levels (basal, 5, 15, 30, 60, 90 and 120 minutes) A descriptive study of the levels of HBCO and of CO (ppm) in the rebreathing circuit was carried out





Results: The peak values of HbCO were obtained in the minute 30 y 60 (Fig. 1) and were different in relation to the desflurane concentration 57 9 ± 05 vs 64 15 ± 5 7, this difference hasn't statistical significance t-test for Equality of Means 95%CI for Diff (–9 907, –2 593). CO peak levels in the circuit was higher in the group of desflurane = 7% but with desflurane 3% the levels were more maintained (Fig 4b)

Conclusion: (1) The CO levels the rebreathing circuits could reach later elevated peaks when low concentration of desflurane were used.

(2) When low desflurane concentrations are used reinhalation and slow production of carbon monoxide are the mainly factors that produce a severe carbon monoxide intoxication.

A.87 Carboxyhaemoglobin concentrations in patients during desflurane anaesthesia using a circle circuit with partially dried soda lime

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Background and Aim of the Study: Routine use of high fresh gas flow (FGF) in circle circuits (>5 L/min) prevents rapid exhaustion of Soda lime (SL) but reduces its water content (1). Dryed SL reacts with desflurane producing high levels of Carbon monoxide (CO) and carboxihemoglobine (HbCO) (2, 3). Nevertheless, very few cases of CO poissoning has been reported in clinical anesthesia We determine the HbCO levels in patients anesthetized with desflurane in operating rooms in which the anaesthesia machine maintained the same SL in place up to 8 weeks, provided that no CO2 rebreathing was observed

Material and Methods: We study 12 consecutive patients scheduled for elective surgery after obtaining their informed consent Anesthesia was maintained with desflurane 7% using a Ohmeda Excell-210 machine and GMS absorber circuit with standard double canister (1.350 g SL each) Two circuits were used: one having SL in place since 4 weeks and another one since 8 weeks. With the 4 weeks-SL circuit, 4 patients were anesthetized maintaining a constant FGF of 7 L/min In other 4 patients FGF was reduced to 2 L/min after 15 min of anaesthesia (when end-tidal desflurane reached 7%) Whith the 8 weeks-SL circuit, 4 patients were anesthetized using a constant FGF of 7 L/min (lower FGF produced CO2 rebreathing). Arterial blood samples were obtained after induction (control) and after 5, 15, 30, 45 and 60 min of anaesthesia. For safety reasons samples were inmediately processed in the operating room for HbCO by cooximetry (OSM3 Hemoximeter, Radiometer, Copenhagen) Water content of SL was determined prior to anesthesia in 50 g samples obtained from the upper, middle and lower layers of the canisters, using a moisture balance (Ohalls MB-200, N Jersey, USA).

Results and Discussion: SL water content (% ± SD), and HbCO (% ± SD) values are presented in the tables In spite of the very low SL water content in the upper and lower layers of the 8 weeks-SL, all HbCO determinations were in the normal range (1–2%) in contrast to the high HbCO levels (up to 50%) found in experimental studies using homogeneous 1.5% dryed SL (2). This can be explained because the higher hydration levels of SL in the middle layer could mitigate the effect of the other layers, avoiding CO production. The capacity of the canister and the flow conditions are factors that play a major role to produce more critical or homogeneous dryness of SL (and could explain the few reported clinical incidents) In fact, we saw that a continuous flow of 7 L/min through a single small SL canister (950 g) for just 41 hours produced a critical dryness level, homogeneously in the three layers (1) But for this to ocurr using the same canister in clinical anesthesia, it would take a longer time than needed for SL exhaustion that will produce CO2 rebreathing earlier. This was observed in our study with the 8 weeks-SL

% water	4 weeks	8 weeks
Upper	8.6 ± 0.2	1.3 ± 0.2
Middle	11.8 ± 0.2	2.5 ± 0.2
Lower	7.1 ± 0.2	1.6 ± 0.2

	%HbCO	Control	5 min	15 min	30 min	45 min	60 min
4 weeks-SL	FGF HI	0.1 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	0.6 ± 0.2
	FGF Lo	0.9 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	0.9 ± 0.2
8 weeks-SL	FGF HI	1.0 ± 0.2	1.3 ± 0.2	1.1 ± 0.2	1.3 ± 0.2	1.0 ± 0.2	1.1 ± 0.2

Conclusion: The use of double high-capacity canisters in circle circuits seems to prevent homogeneous critical dehydration of SL due to long periods of clinical use with high FGF regimes. This could avoid CO production under desflurane anesthesia.

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A.88 Sodium hydroxide is a factor in the production of carbon monoxide when dried soda lime is exposed to desflurane, enflurane and isoflurane

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Background and Goal of Study: The interaction between carbon dioxide absorbents containing strong alkai (sodium hydroxide) and volatile anaesthetic agents has recently given cause for concern (1, 2). A mixture of calcium hydroxide and hydrated calcium chloride ($CaCl_2$ $6H_2O$) containing 10% water has been found to absorb carbon dioxide. The aim of this study was to assess the production of carbon monoxide when desflurane, enflurane and isoflurane were exposed to a dried sample of the above mixture and conventional sodalime.

Materials and Methods: Sodalime (Intersorb™) or the new mixture were heated in an oven at 250°F for eight hours. A gas mixture of oxygen/nitrous oxide in a 50:50 mix at a flow of 1 l/min with desflurane, enflurane or isoflurane at 1 MAC and CO_2 at 40 ml/min was passed through a canister containing 100 g of each absorbent. After 1 minute a 2 1 sample of the gas was collected and analysed for carbon monoxide content

Results: The table shows carbon monoxide content of the collected gas.

	Sodalime	New mixture
Desflurane	600 ppm	1 ppm
Enflurane	580 ppm	1 ppm
Isoflurane	620 ppm	2 ppm

Conclusion: The presence of sodium hydroxide is a factor in the production of carbon monoxide produced when desflurane, enflurane and daesflurane are exposed to dried carbon dioxide absorbents.

Dr C Renfrew was in receipt of a Research Fellowship from the Ulster Hospital, Dundonald, N Ireland.

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A.89 Effect of using dry carbon dioxide absorbent in a rebreathing anaesthesia circuit for sevoflurane

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Background & Goal of Study: It has previously been reported that carbon monoxide forms via reaction between inhalation anesthetics and CO_2 absorbents.[1] Fang's study showed that desflurane, enflurane and isoflurane produced substantial quantities of CO; whereas, halothane and sevoflurane produced only minor quantities of CO. More recently, others have seen enhanced reactions of these anesthetics with very dry CO_2 absorbents, but the analytical results on the degradants produced, in particular Compound A, have been questionable.

Material & Methods: Dry Soda lime (<2.5% moisture) was loaded into two CO_2 absorbent canisters in an anesthesia machine. Thermocouples were placed in the soda lime and at the patient Y tube to record temperature profiles. Datex Gas Monitors were connected to determine the compositions of fresh gas, inspiratory gas and expiratory gas. A flow of 2.2 L/min of 8% sevoflurane was initiated with 7.5 L/min total recirculated volume 0.3 L/min of CO_2 was added to the Y tube to simulate the patient's expiratory gas. Samples of inspiratory gas were taken periodically for 3 hours using gas tight syringes. Samples were tested for carbon monoxide, Compound A and sevoflurane potency using validated GC methods.

Results & Discussion: Parts of the CO_2 absorbent bed reached a temperature of but the highest temperature at the patient mouthpiece was only Forty minutes into the experiment, the top canister had turned dark purple which indicated that the CO_2 absorbing capacity in top canister had been exceeded. The CO_2 detected on Datex Gas Monitors indicated that CO_2 absorbing capacity of both canisters was exhausted at 80 minutes. Carbon monoxide was produced during the first 120 minutes reaching a maximum concentration of 536 ppm at 80 minutes. Compound A does not increase until the CO_2 absorbent is exhausted, reaching a maximum concentration of 68 ppm at 90 minutes.

Conclusion: Our study has demonstrated that the Compound A increase corresponds to the CO_2 absorbent's exhaustion Standard practice suggests that the CO_2 absorbent would be changed before the indicator color change occurs or at least when it is first noticed. To date, there is no clinical evidence to indicate that the generation of Compound A from the reaction of sevoflurane with dry soda lime is of concern

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A.90 Dry soda lime heavily degrades sevoflurane during inhalation induction

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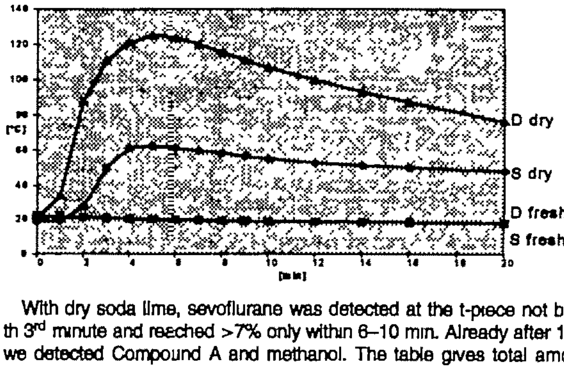
Sevoflurane is partially degraded by hot soda lime (1). Recently (2), there have been two interesting communications:

1) Failure of induction coincident with a remarkably slow rise in concentration at the T-piece despite a high setting of the vaporizer. 2) Severe airway irritation during inhalation induction. To elucidate possible mechanisms we investigated the gas composition during simulated inhalation induction.

Material and Methods: Using a conventional Draeger circle system, 8% Sevo in 6 l/min O_2 were washed into an absorbing canister (1l, Draeger) filled with fresh or dried soda lime with 2.9% (Draegersorb 800, "D") or without KOH (<0.01%, Sofnosorb, Molecular Products, "S"). Drying was achieved simulating possible clinical handling errors (6–15 l/min O_2 for 20–34 hours, total 15000 l). Gas samples were drawn every minute for 20 min at the T-piece. The gas was then directed through bubble flasks to catch hydrophilic degradation products Analyses were performed using GC/MS or FID with appropriate standards (Comp A:sd ± 14%, CH_2OH:sd ± 8%), an ISE (F) and a test kit (H_2CO, Aquamerck)

Results:



With dry soda lime, sevoflurane was detected at the t-piece not before th 3rd minute and reached >7% only within 6–10 min. Already after 1 min, we detected Compound A and methanol. The table gives total amounts (mg) during 20 min.

	Methanol	Formaldeh	Fluoride
S fresh	not detec.	not detect	≥1.9
D fresh	not detec.	not detect	≥1.3
S dry	88	not detect	≥3.3
D dry	789	≥2.3	≥8.5

Conclusion: During inhalation induction with Sevoflurane the use of fresh soda lime is of crucial importance With dried soda lime, the patient may inhale potentially toxic substances in significant amounts. Degradation is aggravated by a high KOH content of the lime. Temperatures above 50°C promote further degradation (3). The observed airway irritation may be caused by formic acid, which is generated in isomolar concentrations with methanol (Cannizzaro-reaction) and not by HF, which reaches the t-piece in low quantities only. The unexpectedly high amounts of Comp A deserve further study

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A.91 Sevoflurane is not degraded during *In vitro* low-flow anaesthesia using a sodium hydroxide-free absorbent

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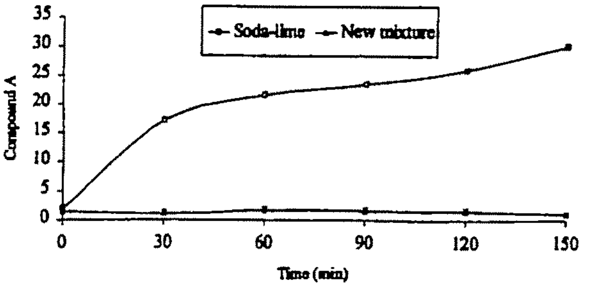
Background and Goal of Study: The interaction between carbon dioxide absorbents containing strong alkali (sodium hydroxide and barium hydroxide) and volatile anaesthetic agents has recently given cause for concern (1, 2) A mixture of calcium hydroxide and hydrated calcium chloride ($CaCl_2.6H_2O$) containing 10% water has been found to absorb carbon dioxide. The aim of this study was to assess the production of compound A during in vitro low-flow sevoflurane anaesthesia using the new mixture.

Materials and Methods: An in vitro experiment was performed where a 50 50 gas mixture of oxygen/nitrous oxide with 1 MAC sevoflurane was flowed through a canister containing either 100 gm of sodalime (Intersorb™) or 100 gm of the new mixture. Three gas samples were removed from an exhaust port distal to the canister at 30 minute intervals into gas tight syringes and were analysed by gas chromatography for compound A concentrations.

Results: The results are shown in the figure as time (min) against compound A concentration parts per million (mean (SD))

Conclusion: Compound A is not produced in an in vitro low flow system containing sodium hyroxide free absorbent for CO_2 absorption.



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A.92 Xenon anaesthesia in humans: expenditure and recycling

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Background and Goal of the Study: The noble gas Xenon (Xe) has been used to perform general anaesthesia since 1946 With the low blood/gas partition coefficient (0.14) and a MAC of 71%, Xe offers rapid induction and recovery from anaesthesia. Moreover Xe shows potent anaesthetic and analgesic properties, it is non explosive, non toxic and it does not undergo biotrasformation. Were it not for high cost, Xe would be a valuable alternative to nitrous oxide. The goal of our study was to determine Xe expenditure and to validate a Xe purifying and recycling system

Material and Methods: 15 patients (8 men, 7 women, age 22–77 years, 52–100 kg, ASA I–II) undergoing abdominal surgery, general anaesthesia lasting 40 to 320 min.

Xe anaesthesia has been performed by two different systems: Modulus Plus Ohmeda (Madison, Wi) (4 patients) and PhysioFlex Drager (Physiomedical System BV, Hoofddorp, NL) (11 patients) Xe was administered via an adapted rotameter The use of a low-flow or a totally closed circuit could permit an easy Xe recycling for the small amount of expired gases, collected in gas thight plastic bags. Moreover Xe uptake breath by breath during anaesthesia with PhysioFlex was obtained by the software Flexcom 5 (Physiomedical System BV, Hoofddorp, NL), also used for other data collection (VO_2, $EtCO_2$, peak, mean and plateau pressure). Xe percentage was also directly measured by a thermic-conducimeter for gas analysis.

A process and an apparatus for purifying and recycling Xe was setup together with SIAD Co. (Bergamo, Italy)

Results and Discussion: In the first 15 min (filling of the circuit after a denitrogenation in Oxygen 100% for 20 min.) Xe expenditure was 11 1 litres, from 15 to 60 min 3 litres, then 3 2 litres for each hour The data show a low supply of Xe after the filling of the circuit, according to the biochemistry and pharmacokinetics of Xe

The result of our recycling technique was a recovery of more than 90% of Xenon

Conclusions: Xe supply and its high cost seems to be the only problem for a routine utilization, In fact Xe is a rare gas present in the athmosphere in a very low concentration Recycling appears as the main solution to all these problems

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A.93 Comparison of isoflurane-clonidine, desflurane-clonidine and sevoflurane-clonidine association in middle ear surgery

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Introduction: Alpha2 agonists are considered as true anaesthetic products Their association with inhaled agents is appraised for the excellent haemodynamic stability induced. This stability is associated with a superficial capillary constriction which offers the surgeon a dry operating site and participate to the success of the procedure One can however regret a marked sedation. Therefore we tried to evaluate desflurane and sevoflurane associated with clonidine in comparison with the association isoflurane-clonidine.

Methods: 60 ASA I or II patients were enrolled The patients were randomised in 3 groups. General anaesthesia was induced with propofol 2 5 mg/kg and sufentanil 0.3 μg/kg Atracurium 0.4 mg/kg was administered for muscle relaxation. Anaesthesia was maintained with isoflurane (group I), desflurane (group D) or sevoflurane (group S) with a mix of O_2/N_2O. After induction every patient received a loading dose of clonidine (4 μg/kg above 30 minutes) followed by a continuous infusion of 1 μg/kg/hr. This infusion was stopped as the graft was positioned Blood pressure and heart rate were recorded every 5 minutes Bleeding was assessed by the surgeon (VAS) at three times incision (T1), dissection (T2), graft positioning (T3). Recovery of cognition and emergence speed were also evaluated Statistical analysis was performed using ANOVA and Chisquare test.

Results: The three groups were comparable according to patients parameters, duration of anaesthesia, operating time, haemodynamic parameters and total doses of propofol, sufentanil and atracurium. Bleeding scores show a significant difference between isoflurane and desflurane with advantage for last one (table1). There was no significant difference concerning times between pure oxygen and extubation, opening eyes or shaking hand. Nevertheless trend for quicker recovery was noted with desflurane (table2).

Conclusion: Whatever the choice is between the 3 inhaled agents, it does not act upon the recovery profile, even though scores in the desflurane group tend to be best. Bleeding appears to be lesser in the desflurane group.

Table 1· Comparison of bleeding in the three groups

	T1	T2	T3
Group I/Group D	0 034	0 001	0 003
Group I/Group S	0 026	NS	NS
Group D/Group S	NS	0 058*	0 023

*Trend for a significant difference

Table 2· Recovery times and emergence profile

Times (min) for	Group I	Group D	Group S	D/I	D/S
Extubation	11.7 ± 4 5	10 4 ± 4 8	13 2 ± 6 5	NS	NS
Opening eyes	11 1 ± 5	9 9 ± 4 7	14 ± 6 4°	NS	0 052
Shaking hand	13 8 ± 7	11 6 ± 4 9	16 ± 7 2°	NS	0 053
Recall birth date	17 6 ± 7 4	15 6 ± 5 6	20.4 ± 9 6°	NS	0 082
Recall room number	· 20 ± 8 8	17 1 ± 7 2	20 9 ± 9 4	NS	NS

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A.94 Influence of somatometric parameters on anaesthesia cost

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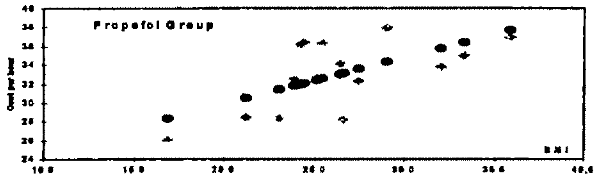
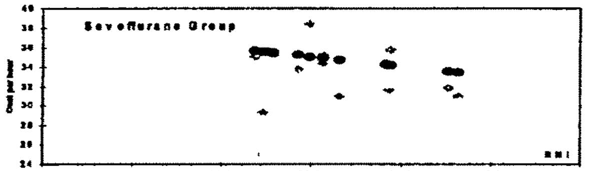
Background and Goal of Study: Cost of anaesthesia tends to affect modern anaesthetic practice. Especially when drugs with short recovery times which do not delay patient's discharge are used, the parameter cost becomes even more important.[1] The following prospective, randomized study was conducted in order to evaluate the cost of two anaesthesia techniques with modern anaesthetics (propofol or sevoflurane) in relation to patient's somatometric data.

Materials and Methods: After approval from the hospital's ethical committee, 30 patients who were to undergo laparotomies under general anaesthesia were randomly allocated to receive propofol or sevoflurane as main anaesthetic agent. Induction to anaesthesia was achieved with propofol supplemented with small doses (10–20 μg) of sufentanil. Anaesthesia was maintained by either continuous infusion of propofol (Propofol group, n = 15) or Sevoflurane (Sevoflurane group, n = 15) both supplemented by nitrous oxide (66%) in oxygen with a fresh gas flow of 6 L/min and sufentanil in incremental doses (10 μg). Cis-atracurium was used for muscle relaxation. Drugs doses and consumption were recorded and cost analysis (in $ US per hour of anaesthesia) was done according to the hospital's current prices. The relation between anaesthetic consumption and Body Mass Index (BMI) was tested with regression analysis test ($p < 0.05$) and corresponding curves were constructed Student t-test was used for comparisons between groups

Results and Discussion: In Propofol group, patients were of 59 ± 16 years of age, with a BMI of 26.3 ± 4.8 and the duration of anaesthesia was 135 ± 17 min. In Sevoflurane group, patients were of 49 ± 11 years of age, with a BMI of 26 6 ± 3.3 and the duration of anaesthesia was 134 ± 24 min. No statistical significant differences were found between groups. In Propofol group (mean infusion rate of 0.6 ± 0 1 mg/kg/min) a positive correlation between BMI and propofol consumption was shown ($p = 0.011$) but in Sevoflurane group (mean concentration in FGF of 1 5 ± 0.2%) no significant correlation was proved ($p = 0.488$).





Conclusion: As the cost of maintenance of anaesthesia with Propofol seems to be related to body weight, and that of Sevoflurane anaesthesia does not, it might be cost effective to choose Sevoflurane in patients with high or above normal BMI and to reserve propofol infusions for patients with low BMI.

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A.95 Elimination of isoflurane, desflurane and sevoflurane after prolonged anaesthesia

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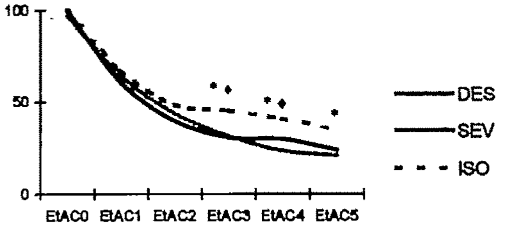
Background & Goal of Study: Desflurane (DES) and Sevoflurane (SEV) shown lower solubility and a theorical faster elimination than other halogenated anaesthetics The aim of this study was to compare the elimination after with DES, SEV or Isoflurane (ISO) anaesthesia in long-lasting open urological procedures.

Material & Methods: Sixty-seven patients ASA 1, 2, 3 were enrolled in this study. Anaesthethic induction was achieved with thiopental, fentanyl and vecuronium After orotracheal intubation the patient's lungs were ventilated with 60% N_2O in oxygen (6 lpm fresh gas flow). The patients were randomly assigned to group DES (n = 23), SEV (n = 22) or ISO (n = 22) for maintenance of anaesthesia and anaesthetic concentration was adjusted to mantain arterial pressure and heart rate within 20% of baseline value. Age, gender, ASA, fentanyl dose, anaesthesia duration, MAC-hours and end tidal anaesthetic concentration (EtAC) at the end of surgery expressec in MAC ($EtAC_0$) were recorded Anaesthetics agents were discontinued and fresh gas flow was mantained with oxygen 100%. Then we recorded the EtAC every minute for five minutes ($EtAC_1$ – $EtAC_5$) expressed in % of $EtAC_0$. Fisher exact test and ANOVA with Bonferroni correction were used for statistical analysis. Data are expressed as mean ± SD and $p < 0.05$ was considered significant

Results: There were no diferences betwen groups in patients age, gender, ASA, total dose of fentanyl, anaesthesia duration, MAC-hours, and EtAC0. EtAC were lower for DES and SEV groups than for ISO group at minutes 3 and 4, and for DES group than for ISO group at minute 5. There were no diferences between DES and SEV groups (figure).



*p <0.05; DES vs ISO at min 3,4 and 5
♦ p<0 05, SEV vs ISO at min 3 and 4

Conclusión: In our experience, both Desflurane and Sevoflurane shown faster elimination after long-lasting anaesthesia than Isoflurane.

A.96 Recovery from anaesthesia with sevoflurane in comparison with isoflurane in elderly patients

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Background and Goal of the Study: From a practical point of view the applicability of sevoflurane in geriatric anesthesia is established. However there are only few data concerning the comparison of sevoflurane with other inhalation anesthetics in this group of age (1, 2, 3) The aim of our study was to evaluate to what extent the recovery from anesthesia with sevoflurane (SEVO) or isoflurane (ISO) differs from each other in elderly patients

Material and Methods: After approval of the study by the institutional review board and after written informed consent has been obtained 50 patients ≥65 years (ASA I–III) scheduled for elective surgery were randomly assigned to receive either SEVO (n = 25) or ISO (n = 25) as inhalation agents for maintenance of anesthesia (1 MAC in N_2O/O_2) Induction of anesthesia was performed with sufentanil (25 μg) and thiopentone (2–4 mg/kg), muscle relaxation with atracurium (0 6 mg/kg). If needed sufentanil (10–20 μg) and atracurium (0.3 mg/kg) were supplemented during maintenance period. The time of recovery events (extubation, emergence, response to commands, orientation, first postoperative analgesia, eligibility for discharge of recovery area) was measured.

Results: There are no statistically significant differences between the two groups, however mean times show a positive trend for SEVO· extubation (9.6 ± 4 84 min vs. 12.2 ± 11 36 min), emergence (9.0 ± 4 84 min vs 10.2 ± 6.16 min), response to commands (11.3 ± 5 71 min vs 13.0 ± 8 21 min), orientation (16.6 ± 7 84 min vs 24.7 ± 30.55 min), eligibility for discharge of recovery area (124 ± 31 39 min vs. 130 ± 35.8 min) The first postoperative analgesic in the SEVO group is administered after 50 3 ± 21.33 min compared to 48.3 ± 23.08 min after ISO.

Conclusion: The recovery period of sevoflurane in elderly patients is comparable to that of ISO with a trend to a faster recovery with SEVO and a later requirement of the first postoperative analgesic after anesthesia with SEVO.

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A.97 Relationship between time of exposure to desflurane, sevoflurane or isoflurane and recovery times in surgical patients

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Background & Goal of Study: Desflurane (DES) and Sevoflurane (SEV) shown lower solubility, lower accumulation in fat tissues and faster emergence times after anaesthesia than other inhaled anaesthetics The aim of this study was to compare the relationship between time of exposure to DES, SEV or isoflurane (ISO) and recovery times in surgical patients.

Material & Methods: In sixty-seven patients ASA 1, 2, 3 anaesthethic induction was performed with thiopental, fentanyl and vecuronium After orotracheal intubation the patient's lungs were ventilated with 60% N_2O in oxygen (6 lpm fresh gas flow) The patients were randomly assigned to group DES (n = 23), SEV (n = 22) or ISO (n = 22) for maintenance of anaesthesia and anaesthetic concentration was adjusted to mantain arterial pressure and heart rate within 20% of baseline value Age, gender, ASA, fentanyl dose, duration of anaesthesia (Danaes) and MAC-hours were recorded. At the end of surgery anaesthetics were discontinued, final end tidal anaesthetic concentration ($EtAC_f$), expressed in MAC were recorded and fresh gas flow was mantained with oxygen 100%. Danaes , MAC-hours and $EtAC_f$ were plotted against time to eye opening, extubation and orientation Fisher exact test and Pearson test for bivariate correlation were used for statistical analysis. Data are expressed as mean ± SD and $p < 0.05$ was considered significant.

Results: There were no diferences betwen groups in patients age, gender, ASA, total dose of fentanyl, anaesthesia duration, MAC-hours and $EtAC_f$ Emergence times were correlated with $EtAC_f$ but not with MAC-hours for DES group Emergence times were correlated with MAC-hours but not with $EtAC_f$ for ISO group. There were correlation between emergence times with MAC-hours and with $EtAC_f$ for SEV group. Recovery times were not correlated with Danaes in any group (table)

Table (values expressing lineal regression "r" for each par)

	DES group			SEV group			ISO group		
	MAC-h	EtACf	Danae	MAC-h	EtACf	Danae	MAC-h	EtACf	Danae
Eyes	−0 02	0 63*	−0 41	0 50*	0 61*	0 37	0 63*	0 63*	0 33
Extub	0.11	0 44*	−0 25	0 63*	0 51*	0 62*	0 10	0 11	0 09
Orient	0 15	0 57*	−0 43	0.36	0 31	0 27	0 50*	0 40	0 25

*p < 0 05

Conclusión: In our experience, emergence times for DES and SEV showed correlation with $ETAC_f$ however emergence times for ISO showed better correlation with MAC-hours Recovery times were not correlated with the duration of anaesthesia in any group

A.98 Emesis and headache after (MAC) in N_2O of halothane, enflurane and isoflurane: outcome following ENT and eye surgery

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Introduction: Isoflurane (I) has superseded halothane (H) and enflurane (E) in usage [1, 2] Emesis and headache may follow general anaesthesia. A literature search revealed no data on the effects on emesis and headache of H, E and I, given for balanced inhalational general anaesthesia.

Methods: With Hospital Ethics Committee approval and patient consent, 556 suitable ENT and eye patients were randomised to receive [MAC] in N_2O of H, E or I. Anaesthesia was strictly standardised except that ENT patients received morphine and eye patients fentanyl as analgesic Postoperatively 'blinded' nurses recorded details of emesis, headache, antiemetic and analgesic requirements Analysis used ANOVA, Chi^2, Students 't' and Mann Whitney 'u' tests ($p < 0\ 05$ significance) Samples >150 per group are required to detect a 10% difference, (95% CI, 80% power).

Results: The 3 study groups were comparable, and comprised comparable subgroups having ear, nose, throat, intraocular or non-intraocular surgery. In the PACU, emesis and drug requirements were similar Thereafter, I induced less emesis than H ($p < 0\ 025$) and necessitated less antiemesis than H or E ($p < 0.005$ both comparisons) Headache and analgesic requirements were similar

	H	E	I
Numbers (M F)	188 (114 72)	186 (114 72)	184 (111.73)
Age (years)	27 (14)	27 (15)	24 (14)
Weight (kg)	51 (21)	48 (20)	48 (18)
Surgical time (min)	59 (29)	54 (24)	55 (27)
Emesis	84 (46%)	76 (41%)	66 (36%)*
Antiemesis	42 (23%)	43 (23%)	21 (12%)**
Headache	65 (36%)	66 (36%)	57 (32%)
Analgesia	132 (72%)	140 (76%)	28 (71%)

Data give as mean (SD) (*I < H, **I < H and E)

Conclusion: Emesis and headache are unpleasant, and the former hazardous, following surgery. Isofluranes favourable pharmacological profile [3] and lesser emetic potential (demonstrated here) endorses its use pending outcome comparisons with sevoflurane and desflurane.

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A.99 Sevoflurane and propofol in surgical patients: comparison of emergence time and psychomotor function

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Background & Goal of Study: The aim of the study was to compare the recovery after sevoflurane (SEV) or propofol (PRO) anaesthesia in intermediate duration surgical procedures

Material & Methods: Thirty patients ASA 1, 2, 3 were enrolled in the study Anaesthetic induction was achieved with thiopental, fentanyl (1–1 5 $\mu g\ kg^{-1}$) and vecuronium The patients were randomly assigned to group SEV (n = 18) or PRO (n = 12) for maintenance of anaesthesia supplemented by 60% N_2O in oxygen (6 lpm fresh gas flow). Fentanyl (1 $\mu g\ kg^{-1}$) was administered before surgical stimulation and anaesthetic concentration was adjusted to mantain arterial pressure and heart rate within 20% of baseline value Age, gender, ASA, fentanyl dose, anaesthesia duration, MAC-hours of SEV and total dose of PRO were recorded. At the end of surgery, anaesthetics were discontinued and fresh gas flow was mantained with oxygen 100% The times to eye opening, spontaneous ventilation, extubation and orientation were recordered A Newman test[1] was performed the day before surgery and at arrival, 20, 40, 60, 90 and 120 min at the PACU Postoperative (PO) nausea and vomiting and the dose of morphine sulfate needed (PCA administration) in 24 hours were recorded Fisher exact test and Student *t* test were used for statistical analysis Data are expressed as mean ± SD and $p < 0\ 05$ was considered significant

Results: There were no diferences betwen groups in patients age, gender, ASA, total dose of fentanyl, anaesthesia duration, PO nausea and/or vomiting, dose of morphine sulphate and Newman's test scores Eye opening time was shorter for SEV group (table)

Table

	Ventilation (min)	Eye open (min)	Extubation (min)	Orientation (min)
SEV	5 0 ± 2 4	7 0 ± 3 5[a]	6 9 ± 3 1	12 5 ± 5 9
PRO	7 3 ± 4 5	11 5 ± 4 8	9 4 ± 4 1	17 5 ± 8 5

[a]p < 0 05

Conclusion: In our experience, the patients who received Sevoflurane only shown faster eye opening after anaesthesia than those who received Propofol. There were no diferences in sensorymotor recovery, side effects or in PO analgesic requeriments in both groups

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A.100 Cognitive recovery after carotid endarterectomy: a comparison of isoflurane *vs* desflurane or sevoflurane anaesthesia

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Introduction: Improved physical properties leading to faster post-operative neurological assessment could make the new inhalational agents desflurane and sevoflurane suitable agents for anesthesia of high risk patients for carotid endarterectomy (CE) In this open label randomized clinical trial, we investigated different post-operative recovery characteristics after CE in patients anaesthetised with either isoflurane, sevoflurane or desflurane

Methods: The protocol was approved by the University Ethics Committee and 75 patients gave informed consent. Anesthesia was induced with propofol 1 mg/kg, alfentanil 15 $\mu g/kg$ and vecuronium 0 08 mg/kg and maintained with equipotent isoflurane, sevoflurane or desflurane concentrations (0.5–1.5 MAC) in 40% of oxygen/air. Surgical and neurological adverse effects were recorded. Postoperative extubation times and times

Time (min) to Communication	Extubation	Conscious Movement	Oral
Isoflurane	13 0 ± 0 8	20 8 ± 0 9	29 8 ± 1 4
Sevoflurane	9 9 ± 0 7	14 0 ± 1 0	20 9 ± 1 5
Desflurane	7 6 ± 0 9	10 4 ± 1 0	16 0 ± 1 4
P-values			
Iso vs Des	**	**	**
Iso vs Sevo	*	**	**
Des vs Sevo	NS	*	*

(** = P < 0 001, * = P < 0 05)

to move consciously controlateral limb and to oral communication were compared Data were expressed a mean ± SE and analysed with ANOVA and paired t-tests P < 0.05 was considered as significant

Results: The three groups (n = 75) had similar demographic variables Duration of surgery and clamping times of the carotid artery were comparable (see table).

Conclusion: Desflurane and sevoflurane provide faster neurological assessment than isoflurane after carotid endarterectomy Recovery times were even shorter with desflurane than with sevoflurane This fast cognitive recovery allows more adequate detection of immediate postoperative complications as neurologic deficits or retrosternal pain.

A.101 Quality and time of recovery from longlasting desflurane or isoflurane anaesthesia

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Background & Goal of Study: Desflurane (DES) is associated with a fast recovery in short duration anaesthesia when compared with other more soluble agents. However is in long-lasting anaesthesia where its properties can be more useful[1]. The aim of this study was to compare the recovery after DES or Isoflurane (ISO) anaesthesia in long-lasting open urological procedures

Material & Methods: In forty-four patients ASA 1, 2, 3 anaesthethic induction was performed with thiopental, fentanyl (1–1.5 $\mu g.kg^{-1}$) and vecuronium. After orotracheal intubation the patient's lungs were ventilated with 60% N_2O in oxygen (6 lpm fresh gas flow) The patients were randomly assigned to group DES (n = 23) or ISO (n = 21) for maintenance of anaesthesia. Fentanyl (1 $\mu g\ kg^{-1}$) was administered before surgical stimulation and anaesthetic concentration was adjusted to mantain arterial pressure and heart rate within 20% of baseline value. Age, gender, ASA, fentanyl dose, anaesthesia duration and MAC-hours were recorded At the end of surgery anaesthetic were discontinued and fresh gas flow was mantained with oxygen 100%. The times to eye opening, spontaneous ventilation, extubation and orientation were recordered. A Newman test[2] was performed the day before surgery and at arrival, 20, 40, 60, 90 and 120 min at the PACU. Postoperative (PO) nausea and vomiting and the dose of morphine sulfate needed (PCA administration) in 24 hours were recorded. Fisher exact test and Student *t* test were used for statistical analysis. Data are expressed as mean ± SD and p < 0.05 was considered significant.

Results: There were no diferences betwen groups in patients age, gender, ASA, total dose of fentanyl, anaesthesia duration, MAC-hours, PO nausea and/or vomiting and the dose of morphine sulphate. Recovery times were shorter for DES group, (table). Newman's test scores were better for DES group only at min 120.

Table

	Ventilation (min)	Eye opening (min)	Extubation (min)	Orientation (min)
DES	5 0 ± 2 1[b]	7 7 ± 3.8[a]	7 9 ± 3 0[a]	12 9 ± 5.0[c]
ISO	7 4 ± 3.2	12.0 ± 4 6	11.0 ± 3 6	18 0 ± 7 3

[a]p < 0 005 [b]p < 0 01 [c]p < 0 05

Conclusión: In our experience, the patients who received Desflurane shown faster recovery from anaesthesia than those who received Isoflurane. There were no diferences in side effects or in PO analgesic requeriments in both groups.

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A.102 Sevoflurane is comparable to propofol for the insertion of laryngeal mask airway in adults

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Background & Goal of Study: The high concentration of sevoflurane used during the rapid inhalational induction of anaesthesia with the single vital capacity breath technique allows the rapid insertion of the laryngeal mask airway (LMA) [1]. This study compares the reliability, quality, and speed of LMA insertion in adult patients anaesthetised with either sevoflurane or propofol

Materials & Methods: 64 unpremedicated ASA I-II patients, aged 18–40, undergoing elective surgery were randomly divided into 2 groups. Patients in the sevoflurane group (n = 34) were instructed to exhale to residual capacity. A facemask connected to a circle/absorber circuit primed for 1 minute with 8% sevoflurane in 66% nitrous oxide (N2O) was then placed and the patients instructed to take a vital capacity breath and hold it as long as possible. 90 seconds later, the jaw of the patient was assessed for degree of relaxation, and if the mouth opening was easy, LMA insertion was attempted. If the jaw relaxation was inadequate, the patient continued breathing spontaneously 8% sevoflurane in 66% N2O Reattempts were made every 30–60 sec for a maximum of 4 times. Patients in the propofol group (n = 30) received iv propofol 3 mg/kg Assessment of jaw relaxation followed by attempted LMA insertion was carried out 60 sec later. Reattempts are made up to 4 times every 30–60 seconds, preceded each time by iv propofol boluses of 0 5 mg/kg.

Results and Discussion: The 2 groups were comparable in age, sex, and weight Anaesthesia was successfully induced in all patients All failures of insertion of the LMA were due to inadequate jaw relaxation

	Sevo	Propofol	
Time to LOC (s)	41 (14)	38 (9)	NS
Successful LMA insertion (%)	100	86 7	NS
Time to LMA insertion (s)	128 (36)	71 (19)	NS
Gag/cough (%)	14 7	28.5	NS
Involuntary movement (%)	17 6	44 8	#
Fall in mean BP %	23 2	24 7	
Pleasant induction (%)	91 1	93 1	NS

#P < 0 05 () denotes SD

Conclusion: Sevoflurane provides a rapid, reliable, acceptable, and haemodynamically stable alternative to propofol for the insertion of the LMA in adults.

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A.103 PCCO monitoring during major surgery

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Introduction: The pulse contour (PCCO) method gives continuous cardiac output values by an arterial pressure wave analysis calibrated with a simple arterial thermodilution measurement. All hemodynamic parameters are monitored through an arterial access and a central venous catheter, without pulmonary catheter, with a lower invasiveness. We compared the cardiac output (CO) obtained from a traditional pulmonary catheter (TD) to the CO obtained with PCCO.

Methods: 20 pts scheduled for lung transplantation (10), liver transplantation (2), general major surgery (4) and thoracic surgery (4) were studied For each patient we analyzed CO in three phases. before surgery (A), during the surgery (B) and at the end of surgery (C). We correlated CO obtained from Swan Ganz catheter and from PCCO catheter (SPSS Plus, PC).

Results: We didn't find significant difference between these two techniques (R = 0.91; R_2 = 0 83) In the following Table values obtained from PCCO and TD in four different surgical procedures, during three phases (A; B; C), are reported

	Lung Tx (10 pts)			Liver Tx (2 pts)		
Phases	A	B	C	A	B	C
PCCO (L/min)	5 4 ± 1 3	5.4 ± 0 7	6 4 ± 1 1	5 4 ± 2 4	3 6 ± 1 0	7 5 ± 0 4
TD (L/min)	4.9 ± 1 4	5 5 ± 0 4	5.8 ± 1 1	5 6 ± 2 1	4 0 ± 1 1	8 6 ± 0 7

	General Major Surgery (4 pts)			Thoracic Surgery (4 pts)		
Phases	A	B	C	A	B	C
PCCO (L/min)	3.6 ± 0 7	7 6 ± 2 6	6 0 ± 2 3	5 1 ± 2 2	6 9 ± 2 4	6 9 ± 2 5
TD (L/min)	4 4 ± 1.8	6 9 ± 4.4	5 5 ± 1 6	5 3 ± 2.0	7 2 ± 2 5	6 9 ± 2 8

Discussion: PCCO through an arterial catheter and a central venous line is able to detect with high correlation CO if compared with standard TD technique, as confirmed by our results.

Conclusions: Pulsion PICCO is an innovative monitoring system that is less invasive than traditional pulmonary artery catheter for thermodilution, is easy to use and safe The results of our study confirm the validity of PCCO and it can be used as a routine monitoring for major surgery.

A.104 Evaluation of PCCO during lung transplantation

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Introduction: Pulsion PICCO is a new monitor, which measures hemodynamic parameters by a beat to beat analysis of the arterial pressure wave calibrated with a simple arterial thermodilution measurement. Using only a central venous catheter and an arterial access is less invasive than the traditional method, which uses a pulmonary arterial catheter. The aim of this study is to compare conventional technique of cardiac output (CO) using a Swan-Ganz catheter (TD) to the measurements obtained with Pulsion PiCCO in pts undergone bilateral sequential single lung transplantation (BSSLTx).

Methods: 10 patients were studied All patients were monitored with a Swan-Ganz catheter and a femoral artery catheter We evaluated CO in six different phases before induction of anaesthesia (A), during the first lung implantation (B), after the reperfusion of the first lung (C), during the implantation of second lung (D), after the reperfusion of second lung (E) and (F) final at the end of the surgery We correlated all CO values obtained from the PCCO and pulmonary artery catheter respectively in all the evaluations for each pt (SPSS Plus, PC)

Results: We didn't find a significant difference between the values obtained from these two different monitors ($R = 0\ 92$; $R^2 = 0\ 84$) In the following Table CO values evaluated with PCCO and TD in five different phases during BSSTx is reported.

Phases	A	B	C	D	E	F
PCCO (L/min)	5 4 ± 1 3	6 6 ± 2.3	6.8 ± 1 7	5 4 ± 0 7	6 4 ± 1 0	6 4 ± 1 1
TD (L/min)	4 9 ± 1 4	6 1 ± 1 7	7 8 ± 2 4	5 5 ± 0 4	6 3 ± 1 0	5 8 ± 1 1

Discussion: PCCO is a new monitor that only after the initial calibration provides continuos CO measurement, it's easy to use, safe and less invasive than Swan-Ganz catheter with a high correlation, as confirmed by our results, even if used in major surgery like BSSTx, in which you can have several artefacts because of surgical heart manipulations.

Conclusions: It will may be use as routine monitoring in alternative to pulmonary arterial thermodilution, even if further clinical evaluations are necessary to confirm our preliminary results.

A.105 Continuous cardiac output: agreement with bolus thermodilution method

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Introduction: Several different approaches for continuous cardiac output monitoring have been developed in recent years Continuous cardiac output (CCO) monitoring system are based on the pulsed warm thermodilution technique Using the same equipment, traditional standard intermittent bolus cardiac output (ICO) values may be obtained by conventional algorithms. The aim of this study was to evaluate the correlation between standard ICO and CCO measurement in patients undergoing coronary artery by pass surgery.

Material and Methods: 15 consecutive patients undergoing coronary revascularization with a hipothermic low-flow, low-pressure cardiopulmonary bypass (CPB) technique were studied. All patients received a conventional narcotic-based anesthetic technique including high-dose fentanyl, midazolam and pancuronium bromide. Cardiac output measurements were accomplished baseline, post-anaesthetic induction, poststernotomy and 15 minutes after the exit of the CBP. CCO was determined immediately before and after ICO measurements, and the average of these two values was recorded as CCO.

Statistical analysis was performed using linear regression for the data pairs, Pearson's correlation coeficient, analysis of agreement to assess bias and distribution of observed differences between techniques according Bland and Altman study.

Results: A total of 60 data pairs were obtained. ICO ranged from 2 to 9.6 L/min, CCO from 2 to 9.2 L/min. The linear regression is represented by: CCO = 0.38 × ICO + 0.71.

Correlation between ICO and CCO was $r = 0\ 71$ ($p < 0.01$). The absolute measure bias was 1.28 L/min with 95% confidence limits ± 2.19 L/min

Discussion: This study has shown a certain discrepancy between the two measure methods of cardiac output These results are in agreement with Siegel[1] and Lefrant studies and in contradiction with those of Yedelman, Boldt[2] and Jakobsen[3]. Consequently, the CCO in comparison with ICO can be a responsible measure of cardiac output More studies would necessary to confirm the clinical interest and to define their indications

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A.106 Clinical implications of continuous automated thermal cardiac output measurement in abdominal aortic surgery

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Introduction: The optimal anaesthetic management of the patient undergoing abdominal aortic surgery remains a major challenge Limited myocardial reserve in most of the cases, due to coexisting coronary disease, in conjuction with the supervening haemodynamic changes resulting from the aortic clamping and unclamping, impose a puzzling problem Selection of the proper monitoring remains a matter of controversy despite recent advances in the field We undertook this study in order to evaluate the efficacy and usefullness of an automated continuous cardiac output pulmonary artery catheter in the intraoperative management of the aforementioned operations.

Material and Methods: Twenty-one patients undergoing scheduled abdominal aortic surgery for atherosclerotic stenosis or aneurysm (7 and 14 respectively) were included to our study All of them had coronary artery disease (CAD) and hypertension under chronic medication, their ASA Physical Status was 3–4 and their age between 47 to 76 years old Premedication consisted of 0.1 mg/kg b w morphine given IM 1 hour preoperatively Pulmonary artery catheterization was performed using a continuous thermal cardiac output catheter that measures also the oxygen saturation of the mixed venous blood (OPTI-Q, Abbott Lab); an arterial line, peripheral pulse oxymetry, electrocardioscopy and end-tidal CO2 were included to the patients monitoring as a standard Heart rate (HR), systemic arterial pressures (SAP, systolic, diastolic), pulmonary arterial pressures (PAP, systolic, diastolic), right atrial pressure (RAP), continuous cardiac output (CCO) and mixed venous saturation (SvO2) were measured on line. Right ventricular end diastolic pressure (RVEDP), pulmonary capillary wedge pressure PCWP) and derived haemodynamic parameters {stroke volume (SV) and stroke index (SI), vascular resistances (SVR, PVR)} were obtained before induction of anaesthesia, after completion of induction, before surgical incision, before and after completion of preparation of the abdominal aorta, after clamping and every 5 minutes till the unclamping of the aorta, immediately after this event and then every 5 minutes Complete haemodynamic profiles were taken in every unexpected event, too Anaesthesia was induced with midazolam (0.18 ± 0 05 mg/kg b w.) and fentanyl (0 010 ± 0 004), muscle relaxation was achieved with vecuronium, and isoflurane plus fentanyl were used for maintenance of anaesthesia. Vasoactive and inotropic agents were used when a greater than 20% change had occurred in one of the haemodynamic parameters or a tendency towards unfavorable haemodynamic profile had been anticipated

Results: A total of 379 sets of measurements were performed, and 315 of them were part of the aforementioned protocol routine, the remaining 64 were dictated by clinical events and criteria other than those included in our protocol, and in 32 of them (50%) the only haemodynamic parameter that showed an alarming decrease (>20%) was the cardiac output without any other sign of haemodynamic deterioration. Only in one case, with a sudden blood loss of about 600 ml, the SvO2 drop preceded the CO decrease The CO decrease in 4 cases preceded an increase of the RVEDP (from 6 ± 2 to 12 ± 3 mmHg) with a latent time of about 45 seconds (45 ± 12 sec)

Conclusions: The use of an automated continuous thermal cardiac output catheter, under the conditions of our study, enables the anaesthesiologist, dealing with major abdominal aortic surgery, to detect decreases in cardiac output that might otherwise go unnoticed since they are not accompanied by any other haemodynamic changes.

A.107 Continuous *vs* intermittent thermodilution cardiac output after cardiopulmonary bypass

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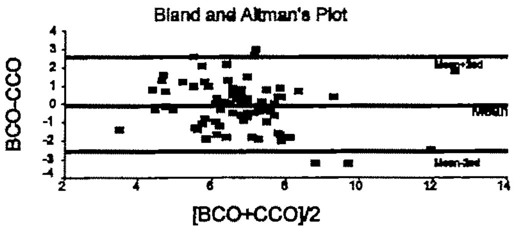
Background & Goal of Study: Thermodilution techniques using pulsed heat to monitor the cardiac output continuously has been recently introduced into clinical practice. Cardiac output measurement by continuous thermodilution techniques has been shown to have a high level of accuracy and precision in critically ill patients and in cardiac surgery patients (1, 2). Both continuous and conventional bolus techniques may fail to agree in the situations of thermal instability (3). We were intersted to analyse the agreement of cardiac outputs measured by both methods in immediate post-cardiopulmonary bypass period in patients undergoing coronary artery bypass graft surgery.

Materials and Methods: After obtaining infromed consent, 12 patients were enrolled in the study. A pulmonary artery catheter (725H, 7 5 FG, Intellicath™, Baxter Edwards, Irvine, CA) was inserted in the conventional manner after induction of anaesthesia and connected to a cardiac output computer (Vigilance, Baxter Health care Corp., IL). After weaning from cardiopulmonary bypass we performed cardiac output measurements at 10 minutes interval and a total of six measurements was taken in each patient Continuous cardiac output value (CCO) was taken as the mean of 2 stat values performed before and after the sequence of bolus injections Bolus cardiac output (BCO) measurements were performed at end-expiration by manually injecting 10 ml of 5% dextrose at room temperature through Co-set (Baxter) and a mean of three consequtive measurements not varying more than 10% from each other was taken Pulmonary artery temperature was recorded at the measurement points. Rapid volume infusion and diathermy were avoided during the measurement period

Results & Discussion: A total of 96 paired data points were taken. Temperature varied from 35.5 to 37 9°C. Data were analysed by Bland and Altman's bias and precision. The absolute measurement bias was −0.11/min and 95% limits of agreement are at 2.57 to −2 59 l/min. Therefore precision was poor and not acceptable The Bland and Altman's plot is shown below

Bland and Altman's Plot



Conclusion: Continuous and bolus cardiac output measurements have poor agreement in immediate post-cardiopulmonary bypass period in patients undergoing coronary artery bypass graft This may be due to thermal instability and increased thermal noise. Further studies are needed to illustrate which method provides values closest to the real cardiac output of the patient

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A.108 Continuous cardiac output and mixed venous oxygen saturation monitoring during cardiac anaesthesia

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Background & Goal of the Study: Nowadays, a modified pulmonary artery catheter is available for continuous and simultaneous monitoring of cardiac output by thermodilution (CCO) and mixed venous oxygen saturation (SvO2) by fiberoptic oximetry. The aim of the study is to evaluate the value of the CO obtained by this method and its relation to the SvO2.

Material & Methods: After informed consent, 18 ASA III–IV patients undergoing cardiac surgery under general anaesthesia with controlled ventilation (FiO2 = 0.5) have been studied prospectively. Non-invasive monitoring and invasive blood pressure were established. Following induction of anaesthesia, a modified pulmonary artery catheter 7.5 F (Edward) was inserted via the right internal jugular vein, using an 8 5 F introducer (Abbott). The catheter was connected to the monitoring device (Vigilance, Baxter). Several parameters were measured 15 minutes after induction (M1), 15 minutes before initiating cardiopulmonary bypass (CPB) (M2) and 10 (M3) and 30 minutes (M4) after leaving CPB. In each patient cardiac output was measured at least three times by injecting 10 ml of room temperature normal saline (BCO) and arterial and mixed venous blood samples were obtained in order to measure SvO2(Co) and to calculate derived parameters. Data are presented as mean ± SD and were evaluated using the T Student test, a simple correlation analysis, and tests of bias and precision

Results: There were not statistically significant differences when CI and SvO2 values measured by both methods in all patients (n = 18, 10 CABG and 8 valve replacements) were compared. Significant direct correlation ($p < 0.01$) between CCOI and BCOI (r = 0.86, bias = 0.07 l/m/m2 and precision = 0.75 l/m/m2), between SvO2 and SvO2(Co) (r = 0 87, bias = 0.44% and precision = 4 73%), between SvO2 and CCOI (r = 0 44), and between SvO2 and BCOI (r = 0.35) exists in all measurements (n = 72). The average CCOI and CBOI values stratification (≤ 2, >2, to ≥ 3 5 and >3 5 l/m/m2) shows that increments in the average value improve bias and decrease precision between CCOI and CBOI, and improve bias and increase precision between SvO2 and SvO2(Co) Increments in the haemoglobin value (Hb > 9 g/%) impair bias and increase precision between CCOI and IBCO, and also between SvO2 and SvO2(Co). Decreases in temperature (<36°C) improve bias and decrease precision between CCOI and BCOI but improve bias and increase precision between SvO2 and SvO2(Co). In M1–M4 measurements, there is significant direct correlation ($P < 0$ 01) between CCOI and BCOI, and also between SvO2 and SvO2(Co) with excellent bias and precision ratios. Significant correlation between SvO2 and CCOI, and between SvO2 and BCOI exists in M1, M2 and M4.

Conclusions: During cardiac anaesthesia: 1) Continuous CO and SvO2 monitoring can be considered accurate, 2) CCOI improve bias and decrease precision for higher CI and T values and for lower haemoglobin values 3) SvO2 improve bias and increase precision for lower CI and T values, while lower haemoglobin values impair bias and increase precision, and 4) Significant direct correlation between SvO2 and CCOI, and between SvO2 and CBOI exists in all results and in three of the analysed moments, except 10 minutes after leaving cardiopulmonary bypass (M3)

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A.109 Comparing methods of cardiac output measurement: oesophageal Doppler *vs* thermodilution

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Objective: To compare cardiac output (CO) measurements precision and accuracy using an esophageal Doppler transducer (ODM-II, Abbott laboratories) versus pulmonary artery catheter, in a wide range of CO values

Materials and Methods: Patients who were considered suitable to insert a pulmonary artery catheter, were addicionally placed an esophageal Doppler transducer. These techniques were carried out by experienced personnel. All patients were normothermic (35 5°–37.5°C). The average of two CO measurements not differing in more than 10%, was taken as value by thermodilution method. The ODM-II value was taken in a period of stable cardiac rhythm with rate under 100 bpm for 4–5 cardiac bates. Two hundred pairs of CO measurements were taken by means of ODM-II and thermodilution. These pairs of measurements were compared against each other. The statistical tests used were lineal correlation coefficient and Bland–Altman test.

Results: The CO (by thermodilution) range was between 2.6 l/min and 10.8 l/min values The ODM-II – thermodilution differences range was between 1.4 and −1 8 values. The lineal correlation coefficient between CO values by ODM-II and by thermodilution was highly significantly: $R^2 = 0$ 9609 ($y = 0.9258x + 0.6197$). Method (ODM-II) precision was determinated by means of lineal correlation coefficient between ODM-II – thermodilution differences values and thermodilution values The result showed a minimun dispersion of values: $R^2 = 0.1408$ ($y = 0$ $0076x - 0$ 074). Comparison of method accuracy was made using Bland and Altman test: the mean of the differences was 0.29, and the 95% limits of agreement were narrow 1.3.

Conclusions: The esophageal Doppler transducer showed a good precision and accuracy with regard to pulmonary artery catheter Although our findings showed that ODM-II had high precision and accuracy during all cardiac output states, this one underestimated cardiac output during low cardiac output estates.

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A.110 Non-invasive haemodynamic monitoring: oesophageal Doppler *vs* thermodilution in cardiac surgery

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Background & Goal of Study: Invasive hemodynamic monitoring is the standard method of measure nowadays the performanceof the cardiovascular system. Pulmonary artery catheterisation has been related with morbidity,: injuries related to central cannulation, pulmonary artery rupture, disrithmias, cardiac blockade asistole and others (1) Futhermore the measurement of cardiac output with thermodilution method provides only intermitent data Transoesophageal doppler ultrasound of descending aortic blood flow, provides an alternative, continuous, noninvasive method of measuring haemodynamic parameters (2, 3)

The purpose of this study was to compare the values of cardiac output (CO) using both methods (thermodilution Vs oesophageal doppler), in cardiac surgery patients.

Material and Methods: 20 patientes underwent cardiac surgery. Haemodynamic registers. **1-Swan Ganz catheter (REF-1, Baxter Lab):** CO, central venous pressure (CVP), pulmonary artery pressure (PAP), Pulmonary wedge pressure (Pw), right end-systolic & end-dyastolic volumes (RESV, RESV), right ejection fraction (REF), right and left systolic ventricular work (RSVW, LSVW), systemic and pulmonary vascular resistances (SVR, PVR). **2-Oesophageal doppler (ODM II, Abbot Lab):** CO, Flow corrected time (FTc), Peak velocity (Pv) and Mean aceleration (Ma) 133 simultaneous registers of those haemodynamic values. Statical analysis: Correlation bivariate, Pearson's test. Significance was acepted for $p < 0$ 05.

Results & Discussion: We have found an excellent correlation on CO values between both methods throughout all study. (CO Doppler 4.65 ± 1.50 lpm Vs CO thermodilution 4.7 ± 1.49 lpm; r2 = 0.839, $p < 0$ 0001). There were a significance correlation between FTc, Pwp ($r = 0.69$, $p < 0.01$), CVP ($r = 0.73$, $p < 0.005$) and SVR ($r = -0.81$; $p < 0.005$).

Conclusions: 1- There was an excellent correlation between both methods respect to CO values 2- FTc is a parameter directly well-correlated with classisc parameters of preload and inversely correlated with afterload.

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A.111 Improved safety during labetalol-induced hypotension by using an oesophageal Doppler for continuous monitoring of cardiac output

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Background and Goal of Study: The purpose of this study was to employ a non-invasive method to monitor continuously alterations of cardiac output (CO) during the use of Labetalol in neurosurgical procedures to ensure its safety

Materials and Methods: Twenty patients, ASA grade I–II, aged 20–60 received general anaesthesia for neurosurgical operations. Total intravenous anaesthesia was induced with propofol, alfentanyl and atracurium. Mild hypotension was induced by Labelatol in incremental doses of 0 5, 0 75 and 1 0 mg/kg to maintain a mean arterial pressure of 60 ± 7 mmHg for a period of 50 ± 10 minutes Haemodynamic monitoring was obtained by E.C G., direct cannulation for arterial and central venous pressures and an oesophageal probe for continuous CO monitoring (ODM II, Abbott)

Results: The changes associated with the hypotension were a slight reduction of the mean estimated CO by 0.57 L/min (4 77 to 4.20), a reduction of mean peak velocity by 9.4 cm/sec (76.8 to 67.4), a remarkable reduction of mean systemic vascular resistance by 347 4 dyn.sec cm–5 (968.7 to 621.3) and a slowing of mean heart rate by 12 beats/min (73.8 to 61.8).

Conclusion: The oesophageal doppler provides a simple and effective method of continuous haemodynamic monitoring to ensure that Labetalol is used safely to obtain hypotension without clinically significant reduction of cardiac output

A.112 Intraoperative control of the efficiency of thoracic sympathectomy for palmar hyperhidrosis by monitoring width pulse waveform and temperature

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Background and goal of study: Primary palmar hyperhydrosis is a benign disorder, nevertheless it may disrupt professional and social life. Endoscopic transthoracic sympathectomy (ETS) is now considered the treatment of choice[1, 2], but currently, no accurate method to asses procedure efficiency during the operation, has been described. The aim of the study was to evaluate intraoperative ETS efficiency by monitoring changes in the width of the pulse wave as well as temperature (T°) in the hand on the sympathectomy side

Patients and methods: Sixty patients scheduled for bilateral ETS were prospectively studied All patients were under general anaesthesia, intubated with a left doble lumen endo bronchial tube and one lung ventilation. Patients were monitored with ECG, invasive arterial blood pressure, SpO_2, end-tidal CO_2 T° was monitored continouosly in both, right and left hand, using a skin sensor placed on each thenar prominence. Record of pulsioximeter wave-form, and hands, T° were obtained after anesthesia induction (BASAL), before T2 sympathicotomy (PRE-SYMP), and at 10 and 20 min post-simpathectomy (10′ and 20′ POSTSYM). The record of difference in temperatures between both hands (ΔTEMP °C) at these times, allows us to discard the influence of anaesthetic or environment factors

Results: An increase in the width of pulse wave superior to 5 mm was observed inmediately after T2 sympathicotomy (left and rigth), In 28 cases (87 5% of patients) The average temperature increase was about 3°C post-sympathectomy (see table)

	Basal	Pre-symp	10′ Post-symp	20′ Post-symp.
TEMP R °C	30 68 ± 2 9	39 91 ± 2 5	32 60 ± 2 2*	33 64 ± 2.2*
TEMP L °C	29 1 ± 2 8	29 06 ± 3 0	31 45 ± 3 8*	32 56 ± 2 2*
ΔTEMP °C Rigth symp	1 58 ± 2 1	1 62 ± 2 4	3 33 ± 2 6*	4 36 ± 2 7*

Mean (± SD) *p ≤ 0 01 Paired student's t-test

Conclusions: Monitoring the width of the pulse wave-form and temperatures is a simple and valid method to control the efficiency of the sympathectomy, since it reflects vasodilation.

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A.113 Premedication with clonidine for laparoscopic cholecystectomy

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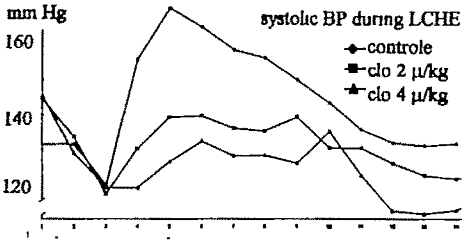
Background and Goals of the Study: Adverse haemodynamic reactions to capnopentoneum during laparoscopic cholecystectomies (LCHE) have been reported The purpose of the study is to demonstrate the effectiveness of a clonidine in prevention of these reactions.

Materials and Methods: After an approval 63 patients elicited for LCHE were randomly allocated into three equal groups. control g. (C) withouth clonidine, and two gps. with clonidine 2 μ/kg (Clo2) and 4 μ/kg (Clo4) resp administered in 100 ml infusion 10 min before induction of general anaesthesia (GA) GA in all groups was performed in a standard way Blood pressure (BP), pulse (P), SaO2 and ETCO2 were measured regularly and at specific phases of surgery (see graph) 1-before clonidine, 2-after clonidine, 3-after induction, 4-beginning of CO2 insuflation (Ins), 5-antiTrendelenburg position (aT.), 6, 7, 8-5 min, resp. 15 min, 30 min after aT, 9-desuflation, 10 end of surgery, 11, 12, 13, 14-1/2, resp 1, 2 and 4 h. after surg The results were tested by Anova Test

Results: There were highly statistically significant differences in systolic BP, MAP, and lower differences in diastolic BP between both clonidine groups and C There was no stastistical difference between Clo2 and Clo4 in suppression of hypertension, but there was higher incidence of bradycardia in Clo4 Less consumption of fentanyl in both Clo groups has been found.



Discussion and Conclusions: Clonidine is an effective agent to prevent adverse sympathetic reaction during LCHE. In spite of some references we did not find beneficial effect of higher doses, on contrary we saw higher incidence of side effects, mainly bradycardia and sedation. We conclude, that i v. clonidine suppresses hypertensive reaction to capnopentoneum in LCHE, the dose 2 μ/kg offers more advanteges than 4 μ/kg Next studies with i m and p.o. clonidine are prepared

The study was supported by IGA MZ ČR, 4142-2

A.114 Effects of age and gender on the optimal administration dose of intramuscular midazolam premedication

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Background and Goal of Study: There are lots of studies about the effects of intramuscular (i.m) midazolam as a premedication However, there are large differences among the studies in the dose and the time of administration. Surprisingly no detailed studies are seen about the optimal dose of i.m. midazolam considering both age and gender. The purpose of this study was to look for the optimal dose of i.m midazolam as a premedication in different age and gender.

Materials and Methods: After the approval by our institutional review board and written informed consent, each 100 males and females in 20 to 39, 40 to 59, and 60 to 79 years (totally 600 patients) were randomly divided into 5 groups according to the midazolam dosage, 0 04, 0.06, 0.08, 0 10, and 0.12 mg/kg Midazolam was injected i m. with atropine 0 01 mg/kg (maximum 0 5 mg) 15 minutes before the induction of anesthesia Blood pressure (BP), heart rate, respiratory rate, percutaneous arterial oxygen saturation (SpO_2), sedation level, existence of the tongue root depression, and eyelash reflex were monitored before and 15 minute after (before anesthesia induction) premedication In addition, anterograde amnesia was checked. Two way factorial analysis of variance followed by Scheffe's F test, Kruskal-Wallis test, and chi-square test were used for statistical analysis P < 0.05 was considered to be significant.

Results and Discussion: Regarding the time of administration, to avoid patients to get the peak effect before enterng the operating room, midazolam was administered 15 minutes before the induction of anesthesia according to our previous study[1]. There were no significant differences between male and female in any parameters in any age. This matched the pharmacological data that showed the difference in only plasma clearance of midazolam, which can not affect acute dose requirements like premedication[2]. Sedation level and amnesia increased according to the increase of age and midazolam dose. Decrease of SpO_2 and loss of eyelash reflex were seen with midazolam 0 10 mg/kg or more in 20 to 39 years, and with 0.08 mg/kg or more in 40 to 59 years In 60 to 79 years, decrease of BP and SpO_2, loss of eyelash reflex, and depression of the tongue root were observed with midazolam 0.06 mg/kg or more Taking side effects into consideration, these doses might be dangerous in some patients

Conclusions: The optimal dose of intramuscular midazolam 15 minutes before anesthesia induction was 0 08, 0 06 and 0 04 mg/kg for 20 to 39, 40 to 59, and 60 to 79 years, respectively, without any differences between male and female

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A.115 Effect of midazolam premedication on implicit memory activation during alfentanil-nitrous oxide-halothane anaesthesia

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Background: Experiences of awareness and recall during general anesthesia can be most distressing for patients. To obtain relevant information, the authors systematically interviewed patients in whom awareness during surgery had occurred and questioned them about their experiences.

Material and Methods: Hundred consenting patients were assigned to two equal groups, to receive 0.08 mg kg^{-1} intramuscular midazolam or normal saline as premedication before general anesthesia with alfentanil-nitrous oxide-halothane During anesthesia, tape containing the test material was played to each patient on a portable cassette player. In the postanesthesia care unit and 24 h after surgery, patients were evaluated using standard questions

Results and Discussion: None of the patients had any recall of events during surgery in midazolam group but one patient in control group was able to recall tape material and another one had experienced nightmare.

Conclusion: We have shown that midazolam 0.08 mg.kg^{-1} given intramuscularly 30 min before anaesthesia prevents activation of implicit memory during alfentanil-nitrous oxide-halothane anaesthesia Since suppression of implicit memory by alfentanil-nitrous oxide-halothane alone cannot be guarenteed we recommend that alfentanil-nitrous oxide-halothane anaesthesia be routinely supplemented with midazolam.

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A.116 Awareness during anaesthesia in patients undergoing cardiac surgery

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Background: The incidence of awareness with recall during general anaesthesia has been reported to be 0.2% (1). In patients undergoing cardiac surgery the incidence seems to be higher. Figures between 1 to 23% have been reported (2) No long-term follow up has been presented in any of these studies The purpose of the present study was to examine the incidence of awareness with recall in anaesthesia during cardiac surgery after four days and three months post surgery

Materials and Methods: After approval from the local ethic committee, one hundred ASA III patients, scheduled for elective cardiac surgery with cardiopulmonary bypass (CPB), gave informed consent to participate in the study. The mean age was 61 years; range 35–79. Premedication was standardised. A balanced anaesthetic technique consisting of midazolam (0.5 ± 0.2 μg/kg/min, mean ± sd) and fentanyl (0 1 ± 0.02 μg/kg/min) was employed. 50% N_2O was added to the O_2/air gas mixture before CPB. Patients were randomised either to isoflurane (0 5–1.5% end-tidal concentration) or propofol infusion (49 ± 19 μg/kg/min) as anaesthetic maintenance during and after CPB. During CPB isoflurane was added direct into the cardiopulmonary bypass system The patients lungs were mechanically ventilated. No muscle relaxant were administered after induction of anaesthesia. Invasive blood pressure, heart rate, body temperature as measured in the urinary bladder, blood glucose, and arterial and venous blood gases were recorded. CPB was performed during hypothermia (30–32 oC) and mixed venous oxygen saturation were kept above 70% Every patient were interviewed four days and three months after surgery and were asked the same questions at both occasions by the same interviewer.

Results: Three out of 100 patients reported awareness with recall after four days. After three months five patients reported awareness. Only one patient out of three with early awareness reported awareness after three months. Interestingly four out of five patients with late awareness were randomised to isoflurane as anaesthetic maintenance as compared to one in the propofol group. However, the difference did not reach statistic significance

Conclusion: Awareness seems to be a problem during cardiac surgery. Adequate concentrations of inhaled or intravenously administered anaesthetics do not prevent awareness and recall completely

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A.117 Need for oxygen supply for patients' transfer from the surgical room to the post-anaesthesia care unit

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Background: At immediate post-surgical period, there is a trend to hypoxemia due to residual effects of anesthetic drugs In order to avoid hypoxemia, almost every patient receive supplementary oxygen at his arrival to PACU. The aim of this study was to evaluate the need of oxygen supply during transfer from surgical room to PACU

Methods: After institutional approval, we studied 70 ASA I/II patients without associated pulmonary nor cardiac pathology, undergoing gynecologic, ophtalmologic or traumathologic surgery under general anaesthesia After extubation, supplementary 100% oxygen was administered during at least 3 minutes until peripheral oxygen saturation (SpO_2) was greater than 94% observed by pulsioxymetry. The patient was moved to PACU breathing spontaneously without oxygen supply, with continuous monitoring of SpO_2 Time of transfer was defined as the time comprised from change from surgical position to bed, until the arrival to PACU. Time of transfer and variations in SpO_2 were measured, evaluating changes from the first value (surgical room) to the last one (PACU) Data are expressed as mean ± SD or median and range Data were analized by paired sample student t test or Wilcoxon signed ranks test as appropiate, with $p < 0.05$ considered statistically significant

Results: Mean age of patients was 51 ± 19 years. Time expended in the transfer was 2′ 51″ ± 35″. SpO_2 in the moment of beginning the transfer was 98% (95%–99%), and at the arrival to PACU was 95% (91%–99%) ($p = 0.0001$) 6/70 (8 6%) patients had a SpO_2 smaller than 92% at the arrival to PACU, with a transfer time of 2′ 56″ ± 21″ ($p > 0.05$). No patient had a SpO_2 smaller than 90% at the arrival to PACU.

Conclusions: Oxygen desaturation is quite common during the transfer from surgical room to PACU. ASA I/II patients without associated pulmonary nor cardiac pathology do not need oxygen supply, although there is a statistically sinificative decrease of the SpO_2 The need of oxygen supply during this period of time must be evaluated patient by patient, mainly regarding associated pathology

A.118 Oculocardiac reflex: is it relevant?

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Background and Goal of Study: Substantial bradycardia due to the oculocardiac reflex is a feared complication of ophthalmic surgery. Although anecdotal reports often refer to this reaction the convincing evidence of the threatening reaction is scarce.

Materials and Methods: In order to asses the autonomic reactivity reflex, tests were performed in 32 ophthalmic patients (mean age 64 years S.D. 17) awaiting for surgery. No ophthalmic patients had history of cardiovascular disease or syncope. Controlled oculopression (OP) of 80 mmHg for 30 sec was applied to both eyes in succession. Subsequently 10 sec carotid sinus massage (CSM) was performed on both sides. The blood pressure was recorded continuously by a photopletysmograph (Finapress 2300).

The ECG was also recorded. Hemodynamic signals were stored and analysed off-line

Results and Discussion: CSM resulted in significant lengthening of RR intervals (Δ RR 230 ms S.D. 239). This response was contrasted by a much smaller though still significant bradycardia elicited by OP (Δ RR 44 ms S.D. 69) The systolic blood pressure decreased following CSM by 26 mmHg (S.D 17). The OP induced systolic blood pressure drop was only 7 mmHg (S.D 12). According to standard definitions hypersensitive carotid sinus response (HCSR) occurred in 4 patients (12 5%). Systolic blood pressure responses on CSM were predictive of OP responses of similar extent ($p < 0.043$).

Conclusions: OP was associated with moderate hemodynamic responses. It is posssible that the tonic eye compression does not reproduce the stimuli imposed by the traction of the extraocular eye muscles occurring during surgery The manual massage of the eyes might have been more representative of the surgical stimuli, however uncontrolled eye compression is not recommended in this patient population As indicated by our results HCSR is a frequent phenomenon among healthy elderly individuals It has been documented that there is an overlap between the neurally mediated syncopal reactions of different origins. Our results substantiate the relationship between the OP and CSM reactions Therefore we suggest that OP test should be replaced by CSM in preoperative assessment of eye surgery patients. Perioperative monitoring of the hemodynamic parameters of the susceptible subject should be recommended

A.119 Is there a correlation between postoperative vomiting and increased extraocular muscle tone in strabismus surgery?

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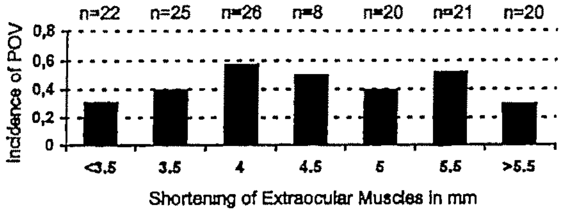
Background: Postoperative nausea and vomiting (PONV) is reported to occur with a high incidence after strabismus surgery It has been suggested that this is related to an "oculo-emetic reflex", arising from extraocular muscle stimulation with a similar pathway to the oculocardiac reflex (1). Therefore, we studied whether the increase in muscle tone caused by a resection or combined recession-resection (RRP) procedure correlates with the incidence of postoperative vomiting (POV)

Materials and Methods: With approval of the local ethics committee 142 ASA 1 to 3 patients undergoing RRP were monitored for POV over 24 hours. Anaesthesia was induced with fentanyl 1.5 μg/kg or alfentanil 15 μg/kg and thiopentone 3–7 mg/kg and maintained with isoflurane or enflurane in O_2/N_2O 1 2 No antiemetics were used. Patients were assigned to one of seven groups according to the resulting shortening of extraocular muscles (in mm). Calculations of patients demographic and surgical data and the incidence of POV were performed with the Chi-square-test and logistic regression analysis $P < 0\,05$ was considered statistically significant

Results: There were no significant differences among the seven groups for sex and PONV in the patient's history, but for age. Therefore, additionally a logistic regression analysis was performed, revealing only age and sex as the main risk factors for POV as reported previously (2). There was no significant correlation between the shortening of muscles and the incidence of POV.



Conclusion: As no correlation between the incidence of POV and the shortening of muscles could be demonstated an increase in muscle tone is unlikely to cause an oculo-emetic reflex.

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A.120 Decisional algorithms for target-controlled infusion of propofol in digestive endoscopy

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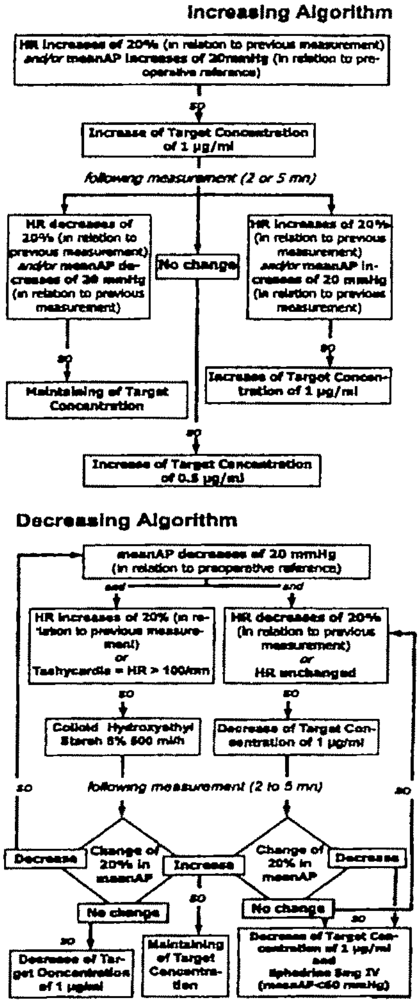
Goal of Study: The development of decisional algorithms for target concentration infusion (TCI) of anaesthetic drugs represents an attempt of adjustment more rational of anaesthesia to the differents levels of stimulation which occur during a surgical or an endoscopic procedure The aim of the study was to verify if it is possible to apply decisional algorithms elaborated to adapt the plasma target concentration (PTC) of propofol during gastrointestinal endoscopy.

Material and Methods: 22 ASA I, II patients, aged 18–65 years, undergoing interventional endoscopic retrograd cholangiography for biliary or pancreatic disease were studied (30 to 205 minutes) Patients were ventilated with an air/oxygen mixture General anaesthesia consisted in a TCI of propofol using the Marsh et al set (1). At the induction, PTC was 3 mcg/ml and every patient received an intravenous bolus of sufentanil (0 1 mcg/kg) and atracurium (0.5 mg/kg) to facilitate intubation After induction we recorded heart rate (HR), mean arterial pressure (MAP) every 2 minutes for 10 minutes and, after, every five minutes until the end of the endoscopy to adapt PTC (figure) We noted the reason of every adjustment of the PTC of propofol.


Increasing Algorithm
HR increases of 20% (in relation to previous measurement) and/or meanAP increases of 20mmHg (in relation to preoperative reference)
so
Increase of Target Concentration of 1 µg/ml
following measurement (2 or 5 mn)
HR decreases of 20% (in relation to previous measurement) and/or meanAP decreases of 20 mmHg (in relation to previous measurement)
No change
HR increases of 20% (in relation to previous measurement) and/or meanAP increases of 20 mmHg (in relation to previous measurement)
so
Maintaining of Target Concentration
so
Increase of Target Concentration of 1 µg/ml
so
Increase of Target Concentration of 0.5 µg/ml
Decreasing Algorithm
meanAP decreases of 20 mmHg (in relation to preoperative reference)
and
and
HR increases of 20% (in relation to previous measurement) or Tachycardia = HR > 100/mn
HR decreases of 20% (in relation to previous measurement) or HR unchanged
so
so
Colloid Hydroxyethyl Starch 6% 500 ml/h
Decrease of Target Concentration of 1 µg/ml
following measurement (2 to 5 mn)
so
so
Decrease
Change of 20% in meanAP
Increase
Change of 20% in meanAP
Decrease
No change
so
No change
so
so
Decrease of Target Concentration of 1 µg/ml
Maintaining of Target Concentration
Decrease of Target Concentration of 1 µg/ml and Ephedrine 5mg IV (meanAP<60 mmHg)

The algorithms were based on our experience of the TCI of propofol during general surgery, on our knowledge of this kind of endoscopy and on recommendations of Everitt (2) Preoperatively, the reference MAP of each patient was determined, particularly in relation to previous hypertension (HT)

Results and Discussion: *First,* we can apply the decisional algorithms in all the patients without any problem for the investigators *Second,* the lenght of the anaesthesia does not interfere with the application of the algorithms, and there is not difference between short (<60 min) and long (>60 min) procedures. *Third,* the algorithms have generated propofol PTC of 3 to 8 mcg/ml and HR and MAP never change more of ± 20% The adjustments of the target concentration correspond with intubation, insertion of the endoscope and sphincterotomy in 77 2%, 31 8% and 22.7% of the patients, respectively Nevertheless, in 68.2%, PTC have been nsed without special event *Finally* the mean PTC required for the intubation (3 77 μg/ml), the endoscopy (4 09 μg/ml) and the sphincterotomy (4 27 μg/ml) do not differ significantly

Conclusion: Decision algorithms can be apply easily during TCI of propofol for digestive endoscopy and permit to rationalize the progress of the anaesthesiology, but it is necessary to know perfectly the endoscopic procedures.

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A.121 Perioperative stress under different regimens of propofol and sufentanil for 'Fast-track'-anaesthesia in cardiac surgery

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Background: Propofol and sufentanil are commonly used for "fast-track"-anaesthesia in cardiac surgery. The prospective randomized study was designed to describe aspects of perioperative stress by using different regimes of total intravenous anaesthesia during surgery. By evaluating psychological and physiological aspects of stress simultaneously the study also asks for the most suitable doses of a propofol-sufentanil combination.

Methods: After approval of the local ethics commitee and written informed consent 72 patients awaiting elective coronary artery bypass grafting were studied. After induction of anaesthesia and endotracheal intubation the group was shifted by a 2 × 3-factorial design for maintenance of anaesthesia by using propofol (1.5 mg/kg/h vs. 2.0 mg/kg/h) and sufentanil (0.014 μg/kg/min vs. 0.021 μg/kg/min vs. 0.028 μg/kg/min). For describing perioperative stress either subjective (coping strategies, thinking about the surgery before and afterwards), either vegetative physiological (heart rate, blood pressure) and either neuroendocrinological (epinephrine, norepinephrine, renin, cortisol, ACTH) parameters were documented.

Results: No group differences were found in baseline-measures. During surgery patients under propfol 2.0 mg/kg/h showed lower expression of ACTH and cortisol after extracorporal circulation. These patients were extubated earlier than patients under 1.5 mg/kg/h propofol, who in tendency need more often rescue medication of propofol and/or sufentanil. There were significant interactions with sufentanil. Patients under sufentanil 0.014 μg/kg/min combined with propofol 2.0 mg/kg/h showed lowest expression of cortisol and ACTH after extracorporal circulation. There were corresponding results in vegetative physiological measurements. Alterations of heart rate and blood pressure were lower under propofol 2.0 mg/kg/h and in tendency lowest under propofol 2.0 mg/kg/h combined with sufentanil 0.014 μg/kg/min. Regarding psychological aspects, patients under propofol 2.0 mg/kg/h showed more positive coping strategies after surgery and in tendency thought more positive two days after surgery. Because of multiple comparisons, the results of the study are considered to be exploratory.

Conclusion: The results of the study indicate that a combination of propofol 2.0 mg/kg/h combined with sufentanil 0.014 μg/kg/min is a suitable regime for "fasttrack"-anaesthesia in cardiac surgery. The study also stresses the importance of a multi-dimensional psychophysiological approach for describing perioperative aspects of stress in cardiac surgery.

A.122 Balanced anaesthesia with remifentanil and propofol; a simplified administration protocol

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Introduction: Remi has a short onset time as well as a short offset of action which makes it a titratable opioid suitable to administer as a continuous infusion. The recommended maintenance dose has an 40-fold range which depends on the combined sedative component and individual patient reactions.[1] A simplified protocol based on the patients body weight and a "50%-rule" (1) was investigated during anesthesia for spondylosis-surgery.

Method: 40 patients were induced with propofol 1.5 mg/kg continued by 3 mg/kg/hr. A remi infusion (50 μg/ml) was started at an infusorspeed (ml/hr) corresponding to the patients' body weight. BP and HR were kept within 15 mm Hg and/or 15 bpm from baseline. Morphine, 0.2 mg/kg iv, was given 30 min before the end of surgery followed by PCA. 20 pat. were ventilated with N2O/O2 and 20 pat. with Air/O2. Maintenance dose, adjustments to the infusorspeed settings and the time to responding and extubation were recorded.

Results: Throughout the operation 1.6 resp. 1.5 adjustments/hr (2) were necessary to maintain an adequate level of anesthesia. With N2O the maintenance dose of remi was significantly lower than in the Air/O2 group. Following the end of surgery patients ventilated with N2O/O2, needed significantly more time to extubation compared to the TIVA group. In the recovery room painrelief proved to be satisfactory within 25 min. Postoperatively no differences between the groups could be registered.

Conclusion: Balanced anesthesia with remi in combination with a low dose of propofol can be administered according the patients weight and a simple 50%-rule. Only 1.5 adjustments/hr are necessary and patients ventilated with N2O/O2 need less remi for maintenance of anesthesia however, recovery is prolonged about 3-fold.

1. 50%-rule:	2. Results (mean/SD)	N2O/O2	O2/AIR
• Prop 1.5 mg/kg	*Average remi dose*	*0.41*/0.18*	*0.51/0.22*
→ 3 mg/kg/hr	(μg/kg/min)		
• Remifentanil speed			
"weight" in ml/hr			
• NMB ⇒ Intubation,	*Remi-speed adjustments*		
reduce remi-speed by 50% ↓	0–30 min	1.8/0.8	2.0/0.7
• Inadeq/excessive anesthesia:	30–60 min	1.1/0.8	0.8/0.9
1st remi 50% ↑ or ↓	60–90 min	0.6/0.7	0.5/0.8
2nd remi previous step 50% ↑ or ↓	overall/hr	1.6/0.7	1.5/0.9
3rd propof 50% ↑ or ↓	*Time to:*		
	response	*7.3/3.2**	*3.1/1.4*
	extubation	*8.6/3.4**	*3.7/1.5*
	(min)	*$P < 0.05$	

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A.123 Remifentanil or fentanyl for carotid artery surgery

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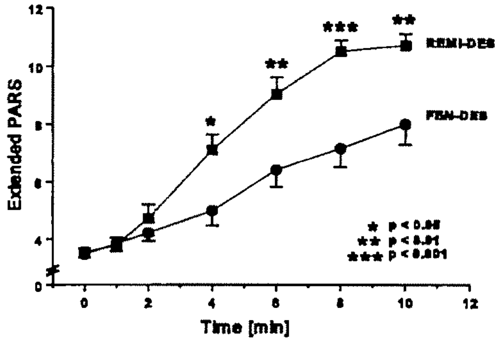
Introduction: Anaesthetic considerations for carotid endarterectomy (CEA) are conflicting regarding the use of opioids: a high-dose opioid technique is recommended because of coexisting coronary artery disease [1], but a low-dose regimen facilitates rapid postoperative awakening and early neurologic assessment [2]. The use of remifentanil may combine profound opioid analgesia intraoperatively with rapid recovery thereafter. Therefore, this study was designed to investigate the emergence profile after remifentanil-desflurane (REMI-DES) compared with fentanyl-desflurane (FEN-DES) anaesthesia.

Methods: With IRB approval and written informed consent patients (ASA II–III) scheduled for CEA were studied at random. Anaesthesia in the REMI-DES group consisted of REMI bolus (1 μg/kg), REMI infusion (0.1 μg/kg/min) and DES (2 Vol% endtidal). Patients in the FEN-DES group received FEN (2 μg/kg) before induction, FEN (2 μg/kg) at skin incision and DES as needed. With termination of surgery anaesthetic delivery was discontinued simultaneously and recovery times were recorded. The postanaesthetic recovery score (PARS) [3] was extended to 12 points including neurologic assessibility. Statistics: Mann-Whitney-U-test ($p < 0.05$); data as mean ± SEM.

Results: A total of 37 patients (REMI n = 18, FEN n = 19) was studied. Recovery times were significantly shorter for REMI-DES than for FEN-DES.

Recovery (min)	REMI + DES	FEN + DES	p-value
Extubation	3.9 ± 0.4	8.4 ± 1.1	0.001
Open eyes	3.7 ± 0.4	8.2 ± 1.2	0.002
State name	6.0 ± 0.7	14.2 ± 2.1	0.001

Furthermore, the patients ability to follow neurologic command testing was faster with REMI-DES than with FEN-DES.



Conclusions: Shorter recovery times and early neurologic assessibility recommend REMI-DES as a suitable alternative to fentanyl-based anaesthesia when used for patients undergoing CEA. These results are most probably explained by the unique pharmacokinetic properties of remifentanil. Additionally, the fentanyl-based anaesthesia regimen had to use higher endtidal concentrations of desflurane. Though desflurane is rapidly exhaled, this may have contributed to the time differences.

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A.124 TIVA without narcotics for anaesthesia under field conditions: interest of ketamine

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Background & Goal of the Study: Under field conditions, narcotics and anaesthesia machine can be difficult to obtain. The aim of this prospective randomised study was to compare a propofol-ketamine TIVA [2] with a inhalation technique or propofol-alfentanil TIVA.

Materials & Methods: After informed consent and institutional approval, 66 ASA I young males were randomly allocated in one of three groups. In group I, anaesthesia was induced with fentanyl 5 μg/kg, thiopental 5 mg/kg, vecuronium 0.1 mg/kg and maintained with isoflurane ≤1% end tidal. In group II, anaesthesia was induced with ketamine 1 mg/kg [1], propofol 2.5

mg/kg, vecuronium 0 1 mg/kg and maintained with propofol 10 mg/kg/h and ketamine 2 mg/kg/h In group III, anaesthesia was induced with alfentanil 30 μg/kg, propofol 2 5 mg/kg, vecuronium 0.1 mg/kg and maintained with propofol 10 mg/kg/h and alfentanil 20 μg/kg/h. All patients were intubated, had controlled ventilation with O_2-N_2O (33–66%) In group I and O_2-air (33–66%) in group II and III Fentanyl (1 μg/kg) or propofol (0.5 mg/kg) boluses were administered when anaesthesia was inadequate. The variation in systolic arterial pressure between preinduction and two minutes after intubation was calculated (ΔSAP) All drugs were discontinued simultaneously at the end of the procedure Statistical analysis included t-test and Anova.

Results: All groups were similar regarding to age, weight, kind of surgery (orthopaedic, general), duration of surgery.

	Group I	Group II	Group III
Duration anaesthesia (min)	69 ± 39	80 ± 30	74 ± 39
ΔPAS %	0 1 ± 1 3	11 6 ± 20*	−9 5 ± 13*
Number of boluses	0 3 ± 0 4*	2 1 ± 2 0	1 5 ± 2 1
Eyes opening (min)	15 ± 5	36 ± 16*	19 ± 7
Extubation (min)	16 ± 5	35 ± 17*	20 ± 7
PACU stay (min)	101 ± 29	131 ± 45*	98 ± 20

mean ± SD, *$p < 0$ 05 versus two others groups

In the PACU, EVA pain score at 30 min was higher in group II (3 3 ± 2 group I, 4.2 ± 2 group II, 3.4 ± 2 group III) whereas duration before first analgesic requirement (median 15, 37, 15 min) and % of patients requiring morphine (14, 27, 14%) were not statistically different.

Conclusions: Propofol-ketamine TIVA, although not better than the other general anaesthesias studied here, appears a suitable technique when the usual anaesthesic equipement or narcotics are not available. In clinical practice, titration of doses to effect may allow a more satisfying course of anaesthesia

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A.125 Bispectral index: a decision or a problem of an estimation of anaesthesia depth?

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An estimation of adequacy and depth of anaesthesia remains one of the basic problems in modern anaesthesiology. In last time a parameter, allowing to supervise intraoperational condition of patient's CNS, named bispectral index (BIS), has become applied. (1). But as this method is based on the spectral analysis EEG, it is quite possible, that it is not deprived of lacks, inherent in similar methods (2). The purpose of this research was to compare informativeness of bispectral index during different kinds of anaesthesia.

Materials & Methods: Three randomized groups of patients (10 in each group) undergoing abdominal surgery has been investigated. 1)-TVA (propofol/fentanil); 2)-general combined anaesthesia (isoflurane/fentanil); 3)-TVA (ketamine/fentanil). Bispectral index was recorded by the A-1000 (Aspect medical system ink., USA) Besides the control of hemodynamic parameters, for comparison of an estimation of anaesthesia depth SSEP's were monitored by the Nomad –3600 (Tracor Norther Ink, USA)

Results & Discussion: In 1) and 2) groups informativeness of bispectral index about anaesthesia depth and adequacy has appeared rather high and coincided with changes early SSEP's. Percent of concurrences was equal 80 in first and 70 the second groups In the third group bispectral index in most cases specified on patients awamess, while SSEP's and hemodynamic parameters informed on sufficient anaesthesia depth Percent of concurrences was equal 20.

Conclusion: Bispectral index is an effective parameter for an estimation of depth during propofol/fentanil and isoflurane/fentanil anaesthesia, but is not effective during ketamine/fentanil anaesthesia Thus at all advantages of this method it is impossible to recommend it as a universal method of an estimation of anaesthesia depth

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A.126 Informational saturation of EEG *vs* bispectral index of EEG

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The gold standard allowing to correspond EEG changes with anaesthesia depth is not yet found We attempt to decide this problem by monitoring of original informational EEG parameter named as an informational saturation of EEG (IN EEG)

Materials & Methods: Three randomized groups of patients (10 in each group) undergoing abdominal surgery were investigated 1)- TVA (propofol/fentanil); 2)- common combined anaesthesia (isoflurane/fentanil), 3)-TVA (ketamine/fentanil) Comparison of sensitivity of an offered method was carried out with bispectral index (A-1000 Aspect medical system ink , USA) and Auditory EP's (Nomad-3600, Tracor Norther ink., USA)

Results & Discussion: In the first and in the second groups investigated parameters correlated good with anaesthesia depth Factor of correlation was 0 87 for IN EEG and 0.81 for bispectral index Between two methods factor of correlation was 0 75 In the third group factor of correlation between anaesthesia depth and IN EEG was 0 71 v s 0 10 at bispectral index There was no correlation between investigated parameters

Conclusion: It is possible to assume, that both methods rather precisely reflect depth of anaesthesia during propofol/fentanil and isoflurane/fentanil anaesthetic technique, but during ketamine/fentanil anaesthesia bispectral index loses the informativeness, while the IN EEG allows to supervise anaesthesia depth However, the reason that influences on the informativeness of researched methods in one or another case was not revealed This is the main problem which constrains wide using of researched methods in automatic control of anaesthesia depth.

A.127 Bispectral EEG monitoring of deep breath inhalation induction of anaesthesia with sevoflurane

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The introduction of sevoflurane has renewed the interest in the concept of mask induction in adult patients Because of its low blood-gas solubility and its nonpungent character, sevoflurane could be used both for induction and maintenance of anesthesia in adult patients. The objectives of this study were to observe the pharmacodynamic characteristics of sevoflurane inhalation induction. Bispectral analysis of the EEG is a signal processing technique that has been proposed as a pharmacodynamic measure of anesthetic effects on the central nervous system. It has been largely demonstrated that an empirically derived bispectral EEG measure, the bispectral index (BIS) is a significant predictor of depth of anesthesia

Methods: After approval of the local ethical committee, forty ASA I or II pts, scheduled for elective outpatient gynecologic surgery were included For induction, a deep breath inhalation induction (after maximal expiration) with sevoflurane 8% and a O2/N20 mixture (35/65%) was applied After loss of consciousness (LOC), sevoflurane was decreased to 4% and anesthesia was further maintained with sevoflurane in a O2/N20 mixture (35/65%) Further adjustment of sevoflurane administration was made according to clinical reactivity

Results: Anesthesia was succesfully induced in all pts. The time to LOC was m45 sec (SD 18 sec) at an ET Sevo of 4 8% (SD 1 7%). BIS started to decrease at the time of LOC reaching a minimal value at a mean of 40 sec later Mean BIS reached after induction was 24 (SD 13). At surgical stimulation (mean BIS of 39, SD 10 and mean ET sevo of 2 9% SD 0 8%) 8 pts had clinical signs of inadequate anesthesia. In all 8 pts, BIS was above 45 and showed a significant increase (+20%) in response to surgical stimulation

Conclusion: Loss of consciousness after sevoflurane deep breath inhalation induction occurred at a mean of 45 sec for an ET sevo around 4 MAC, which is higher than previously reported for quiet breath sevoflurane inhalation induction. The BIS value was an excellent predictor of reaction to surgical stimulation, as all pts with a BIS above 45 reacted to surgical stimulation in a sevoflurane/O2/N2O anesthesia.

A.128 Patient-tailored sevoflurane anaesthesia guided by bispectral EEG

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The Bispectral Index (BIS) has been shown to be a quantifiable measure of the effects of anesthetics on the central nervous system. Previously, titration of anesthetics was guided by knowledge on dose-response curves for anesthetics and by clinical reactivity to noxious stimulation. In the present study, we tried to assess the anesthetic requirements when using a BIS-guided sevoflurane anesthesia

Methods: Twenty unpremedicated ASA I or II pts scheduled for laparoscopic abdominal surgery were studied Anesthesia was induced with 8% sevoflurane deep breath inhalation and N2O/O2 (65/35%) After induction of anesthesia, sevoflurane (in a N2O/O2 mixture: 65/35%) was adjusted in order to maintain BIS between 45 and 55. No intravenous opioids were administered (local infiltration of surgical wounds was performed by surgeon). From 10 min after induction (achieving a stable level of anesthesia) until 10 min before skin closure (when BIS was allowed to return to 60–75) all end-tidal (ET) sevoflurane concentrations were recorded per minute and a mean value/minute was calculated.

Results: Using a BIS-guided sevoflurane mono-anesthesia, mean anesthetic requirement was 1.76% ET sevo (SD 0.78) or a mean of 1.5 MAC. We observed a wide inter-individual range in required anesthetics between a mean of 0 98% and a mean of 4.4% ET sevoflurane required to maintain a peroperative BIS between 45 and 55.

Conclusion: Using a BIS-guided sevoflurane mono-anesthesia in unpremeditated pts we found a large inter-individual variability (fourfold difference) in anesthetic needs, demonstrating that EEG-BIS monitoring might be useful in improving the titration of volatile anesthetics

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A.129 Clonidine pretreatment does not reduce anaesthetic requirements in bispectral EEG-guided sevoflurane anaesthesia

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Clonidine is an alpha2-adrenergic agonist with sedative-hypnotic and analgesic properties. When used as adjuvants in general anesthesia, alpha2-adrenergic agonists are reported to reduce anesthetic requirements. Previous studies have demonstrated that an emperically derived EEG measure, the bispectral index (BIS), is a significant predictor of depth of anesthesia. We conducted a placebo controlled trial to assess the anesthetic effects of clonidine. Therefore, the anesthetic requirements in a BIS-guided sevoflurane anesthesia in pts pretreated with clonidine were analysed.

Methods: Twenty ASA I or II patients scheduled for laparoscopic abdominal surgery were investigated. Pts were unpremedicated and were randomly allocated to receive either intravenous saline solution or clonidine 3 μg/kg in a saline infusion over a 10 min period, 15 min prior to anesthesia. Anesthesia was induced by 8% sevoflurane deep breath inhalation and was maintained by sevoflurane in a mixture of N20/02 (65/35%) in order to maintain a BIS between 45 and 55. All surgical incision wounds were locally infiltrated (with bupivacaine) by the surgeon. From 10 min after induction (achieving a stable level of anesthesia) until 10 min before skin closure (when BIS was allowed to return to 60–75) all end-tidal (ET) sevoflurane concentrations were recorded per minute and a mean value/minute was calculated. Differences in anesthetic requirements (ET sevo) were analysed with a Wilcoxon signed rank test.

Results: Both groups were demographically similar with no significant differences between them in terms of age, weight or height, or in operative time (mean of 51 min). Mean anesthetic requirements in placebo pretreated pts were not statistically different from clonidine pretreated pts (1.79 ET sevo (SD 0.76) for placebo group vs 2 05 ET sevo (SD 0.94) for clonidine pretreated group).

Conclusions: Using a BIS-guided sevoflurane anesthesia, we were not able to conclude to a reduction in anesthetic requirements after clonidine pretreatment

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A.130 Bispectral index and calculated plasma concentrations of propofol and sufentanil during emergence from target-controlled anaesthesia

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Background and Goal of the Study: The Bispectral index (BIS) is a new processed EEG variable correlated with the hypnotic effect of anesthetic agents. The present study was designed to analyse BIS and calculated plasma concentrations of propofol (PPF) and sufentanil (SUF) during emergence from target-controlled anesthesia.

Materials and Methods: After approval by the Ethics committee, we studied 28 ASA I or II consenting patients, scheduled for elective surgery under general anesthesia. Premedication consisted in 1 mg alprazolam given orally 1 h before surgery. Anesthesia was induced and maintained with PPF and SUF using a computer-controlled infusion device. Tracheal intubation was facilitated with atracurium and ventilation was controlled with air/oxygen. The end-tidal CO_2 was maintained close to 30 mmHg and rectal temperature remained above 35.5°C throughout the study. After completion of surgery, BIS values and calculated plasma concentrations of PPF and SUF were recorded at the following patient's recovery steps: recovery of spontaneous breathing (SB: respiratory rate $>8\ \text{min}^{-1}$ and end-tidal $CO_2 <$ 45 mm Hg), eye opening (EO) to command, and recall of birthday (BD). BIS values and calculated plasma concentrations of PPF and SUF at the different steps of recovery were analysed using repeated measures ANOVA. The calculated plasma concentrations of PPF and SUF were fitted by regression analysis at each end point. The prediction probabilities of the degree of recovery were also determined for BIS and the calculated concentrations of PPF and SUF (1). $P < 0\ 05$ was considered statistically significant

Results: Results were expressed as means (SD). Calculated plasma concentrations of PPF and SUF decreased significantly and BIS increased significantly from SB to EO and from EO to BD (table). A significant correlation was observed between PPF and SUF concentrations at SB, EO and BD (r = 0 55, 0.65, 0 62), respectively. The prediction probability was 0.94 (0.13) for PPF, 0.92 (0.15) for SUF and 0 89 (0 16) for BIS

	SB	EO	BD
Calc PPF conc (μg/ml)	1 78 (0 35)	1 62 (0 28)*	1 46 (0 21)#
Calc SUF conc (ng/ml)	0 080 (0 007)	0 079 (0 007)*	0 076 (0 007)#
BIS	72 5 (12 8)	77 9 (12 0)*	92.4 (6 6)#

*significantly ≠ from SB, #significantly ≠ from EO and SB

Discussion: BIS values and calculated plasma concentrations of PPF and SUF changed significantly during the different steps of recovery. The high correlation observed between PPF and SUF at each end point might be ascribed to individual variability in drug response and could reflect the absence of drug interaction in their range of concentrations. When considered alone, the calculated concentration of PPF provided a better prediction of recovery than the calculated concentration of SUF and BIS

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A.131 Variations of bispectral index during peroperative movements and recovery from isoflurane anaesthesia

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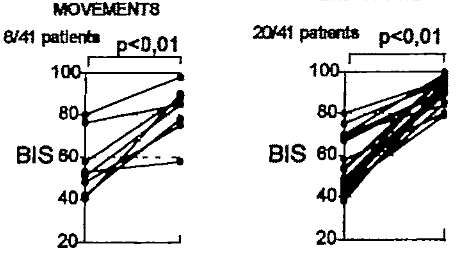
Background: Previous studies demonstrated that bispectral index (BIS) monitoring can be used to assess the hypnotic effects of anesthetics[1]. Values superior to 90 assess awaking. The time of calculation of BIS – 40 seconds – don't make it a real instant EEG parameter. The present study evaluated BIS variations during peroperative movement and during end of isoflurane anaesthesia.

Material & Methods: After institutional approval, we studied 41 ASA 1 or 2 patients scheduled for general surgery. All patients received induction using propofol (2–3 mg/kg) and sufentanil (0.2 mcg/kg). Vecuronium (0.1 mg/kg) was used to facilitate intubation. Patients breathed N_2O/O_2 (FIO_2 = 0.5). BIS (Aspect Medical System A-1000 EEG monitor) was recorded every 5 seconds and was blinded to the anaesthesia provider. When a patient present an intraoperative movement, time was noted at the second BIS values at the movement (mvt) and one minute after (mvt + 1 min) were analysed. The pulse rate, MAP were also monitored. Data were analyzed using Student's t-test or Chi square test. $P < 0.01$ was considered significant

Results: 8/41 patients presented peroperative movement, BIS at this time was 56 ± 16, compare to 82 ± 11 one minute after (mean ± sd, Figure 1 A). At the end of anaesthesia, half of the patients present rapid variation of BIS: 55 ± 12 to 87 ± 11 in one minute (Figure 1 B). In the other patients BIS values progressively reach 90.



Conclusion: Peroperative variations of BIS under isoflurane and low dose sufentanil could be rapid, with an increase of surgical stimulation, or with a constant stimulation: orotracheal tube at the end of anaesthesia. These data suggest that interpretation of BIS is time dependant, and clinical situation has to be taken into account.

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A.132 Dose-response relationship between target-controlled concentration of propofol and bispectral index

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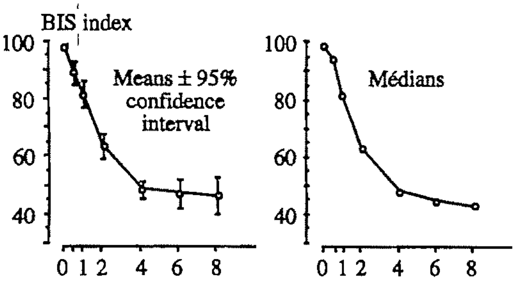
Background and Goal of Study: Bispectral index (BIS) allows a quantitative EEG measure of anesthetic effect Recently, Leslie et al (1) showed that BIS linearly relates to propofol blood concentration in volunteers. This study was designed to characterize the relationship between propofol target-controlled concentration and BIS in surgical patients

Material and Methods: 30 consenting males (ASA I–II, 18–50 yr, 50–80 kg) having elective urogenital surgery were studied before surgery, after institutional committee approval. After oral diazepam (0 2 $mg.kg^{-1}$), each patient was administered a dose-ranging sequence of propofol using a computer-controlled infusion device (STELPUMP) Assigned target site effect concentrations of 0, 0.5, 1, 2, 4, 6 and 8 $\mu g\ ml^{-1}$ were maintained for 3 min. EEG was acquired from a bifrontal montage using the Aspect A-1000 monitor™ (Spacelab). Electrode impedances were maintained below 5000 ohms. BIS was recorded on a 15 s basis during the 3rd minute of steady state, using the 4D software (Macintosh). Each BIS score was the average of 4 recorded values Statistical analysis was made using linear regression analysis Data are presented as means ± 95% CI and medians

Results and Discussion:

(1) BIS was linearly related to propofol target site effect concentration in the concentration-ranging 0–4 $\mu g.ml^{-1}$ (BIS = −12 5 * [target] + 99.8, r = 0 87; n = 150).

(2) The target concentration of 4 $\mu g\ ml^{-1}$ produced a mean BIS score of 47 (CI 44–50), indicative of hypnosis Further increases in target concentration did not affect BIS significantly, due to the anesthetic interventions required for maintaining adequate airway. Manual ventilation was needed in the range of 4.8–7 6 $\mu g\ ml^{-1}$



Target effect site concentration ($\mu g.mL^{-1}$)

The estimated value of BIS_{95} for loss of consciousness with propofol is 51 (95% CI 48–55) (2) Based on the relation of BIS to target concentration, our data suggest that a target site effect concentration in the range of 3.6–4.1 $\mu g.ml^{-1}$ correlates with BIS_{95}.

Conclusion: The target-controlled site effect concentration of propofol required to induce anesthesia arounds 4 $\mu g\ ml^{-1}$ in healthy male patients premedicated with diazepam

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A.133 Matching sympathetic response of visceral pain with propofol target-controlled infusion: a blinded bispectral study

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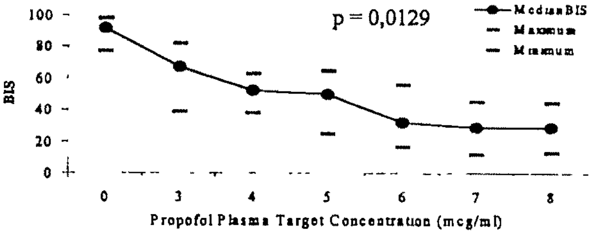
Goal of Study: The digestive endoscopy corresponds to a pure visceral pain with sympathetic stimulation and excludes the other afferences (skin, wound and articulations). In a recent multicenter study, Sebel et al (1) have proven that the Bispectral encephalogram analysis (BIS) correlates best with the effects of primary hypnotic-based anaesthetic techniques. The aim of the study was to verify, in case of a pure visceral pain, the correlation between the plasma target concentration (PTC) of propofol and the BIS.

Material and Methods: 22 ASA I, II patients, aged 18–65 years, undergoing interventional endoscopic retrograd cholangiography for biliary or pancreatic disease were studied (30 to 205 minutes). Premedication consisted in intramuscular 0.1 mg/kg of midazolam 30 minutes before endoscopy. Patients were ventilated with an air/oxygen mixture. We used a TCI of propofol with the Marsh et al set (2), and the initial PTC was 3 mcg/ml. Every patient received at induction intravenous sufentanil (0.1 mcg/kg) and atracurium (0.5 mg/kg) to facilitate intubation. We used decisional algorithms to modify the PTC of propofol based on the heart rate (HR) and the mean arterial pressure (MAP) trends BIS was recorded every 2 minutes for 10 minutes, and after every 5 minutes until the end of the endoscopy, but it was hidden from view of the investigators, and so, could not interfere with the anaesthesia progress. First, we determined the median of the recorded BIS for the different observed propofol PTC in every patient. Second, the median of these 22 median BIS was calculated for every PTC (figure). The minimal and the maximal calculated values of the median BIS for each PTC represent the dispersion of the measures (figure)

Results and Discussion: Decisional algorithms have generated propofol PTC of 3 to 8 mcg/ml.



Using the Friedman test, the different levels of BIS are statistically differents for the observed PTC of propofol, and even in case of a pure visceral pain, the results are comparable to these ones of Sebel et al (1) published for skin and wound incision The median BIS at the induction (92) probably reflects the effect of premedication. Moreover, data analysis permits to calculate the median BIS for the intubation, the insertion of endoscope and the sphincterotomy (62, 58.25 and 52 5 respectively)

Conclusion: Our results show a correlation between the BIS and the PTC of propofol even in case of pure visceral stimulations and the BIS can be considered as an acceptable index of the cortical effect of the anaesthesia.

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A.134 Improved anaesthetic titration using the bispectral index of the EEG in malignant obese patients

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Dose-response relationships for anesthetic drugs and clinical reactivity (changes in autonomic and somatic responses) to noxious stimulation are todays clinical guide to titrate anesthetic drugs Bispectral analysis of the EEG is a signal processing technique that has been proposed as a pharmacodynamic measure of anesthetic effects on the central nervous system The Bispectral Index (BIS), an empirically derived bispectral EEG measure, was reported as a significant predictor of depth of anesthesia. This prospective, randomized study assessed the effects of a BIS-guided anesthesia on anesthetic requirements in malignant obese patients

Methods: Thirty female ASA I or II pts with a BMI greater than 40 and scheduled for laparoscopic gastric banding were included Pts were randomly allocated to receive standard clinical practice (SP) or BIS-guided anesthesia. In both groups anesthesia was induced with propofol (1 mg/kg), alfentanil (50 $\mu g/kg$) and cisatracurium (0 15 mg/kg), to facilitate endotracheal intubation. Anesthesia was maintained with propofol (6 mg/kg/hr), alfentanil (40 $\mu g/kg/hr$) and N2O/O2 (65/35%) In the SP group, anesthesia was titrated by clinical reactivity to noxious stimuli (increase or decrease of propofol and alfentanil with 10%), while in the BIS-group anesthesia was guided to maintain a BIS between 45 and 55. Out of these borders, propofol and alfentanil were increased or decreased with 10%. Statistical analysis was performed using a Wilcoxon ranked test.

Results: Both groups were demographically similar with no significant differences between them in terms of age, weight or height, or in operative time. Total anesthetic administration was significantly lower in the BIS-group compared to the SP group. Mean need of propofol and alfentanil was, respectively 6.3 mg/kg/hr and 41.5 $\mu g/kg/hr$, in the SP-group, while in the BIS-group mean need of propofol was 4.8 mg/kg/hr and 32.5 $\mu g/kg/hr$ of alfentanil. A large variation in anesthetic requirements was observed in the BIS-group with a range between 3 2 to 7.8 mg/kg/hr for propofol and 24 to 52 $\mu g/kg/hr$ for alfentanil.

Conclusion: Anesthesia guided by BIS resulted in the administration of less anesthetics. Especially in patients with an increased body weight, titration of anesthetics to pharmacodynamic effects might result in a superior anesthetic management.

A.135 Bispectral index of EEG does not predict haemodynamic responses to laryngoscopy and intubation under sevoflurane anaesthesia

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The Bispectral index (BIS) has been reported as a significant predictor of depth of anesthesia. Earlier reports have indicated that a BIS below 50, after induction of anesthesia, is consistent with an adequate level of anesthesia. The aim of this report was to observe the cardiovascular responses on intubation after sevoflurane inhalation induction in pts revealing an adequate depth of anesthesia (BIS below 50).

Methods: Thirty pts scheduled for out-patient surgery were included. For induction, a deep breath inhalation induction with sevoflurane 8% in a O2/N2O mixture (35/65%) was applied. After loss of consciousness, sevoflurane was decreased to 4%, ventilation was assisted and cisatracurium (0.15 mg/kg) was given to facilitate orotracheal intubation Bispectral EEG monitoring was performed in a bifrontal referential montage using an Aspect-1000 EEG monitor. BIS, heart rate (HR), systolic and diastolic blood pressure (SBP, DBP) were recorded before induction (base), just before intubation, and at their heighest value within 2 min after intubation. Intubation was not attempted until BIS was lower than 50

Results: Anova was used for statistical analysis and values are shown as mean and standard deviation (SD).

	Base	Pre-intub	Post-intub
BIS	96 1 (2 0)	30 (8.5)	44 5 (9 7)
SBP	128 (13 5)	104 (10 2)	50 2 (18 8)
DBP	79 (16 5)	64 (12.7)	103 (18 6)
HR	79 1 (13 8)	76.4 (10 8)	93 (12 7)

Although BIS was below 50 in all pts before attempting intubation, SBP, DBP and HR increased significantly after intubation compared with the baseline values There was a good correlation between increases in hemodynamic parameters and increase in BIS, reflecting the cerebral cortex activity on intubation

Conclusions: These results indicate that sevoflurane inhalation anesthesia is not effective to prevent hemodynamic responses on intubation at anesthetic depth of BIS within 30 (SD 8.5). Therefore, BIS can not predict the hemodynamic responses to intubation under sevoflurane anesthesia.

A.136 Comparison of SEF and BIS by using two devices for electroencephalography under different regimens of induction of anaesthesia in cardiac surgery

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Background: The EEG bispectral index (BIS) is considered to be a sensitive parameter for describing as well depth of anaesthesia as well lost of consciousness. So the BIS might be also suitable for monitoring induction of anaesthesia in high-risk-patients, where titration of the drugs used is very important to avoid complications. It has to be asked, whether the BIS is comparable or probably more suitable than other EEG-markers, such as the spectral edge frequency (SEF) Thereby a bias of two different devices for calculating the SEF has probably to be taken into account. The prospective single-blinded randomized study was designed to evaluate different regimes of induction of anaesthesia in cardiac surgery by using the BIS and SEF of two different devices.

Methods: After approval of the local ethics commitee and written informed consent 48 patients awaiting elective coronary artery bypass grafting were studied. Four different regimes for induction of anaesthesia were used:

Regime 1: Continuous application of Midazolam (4 Minutes) up to 0.07 mg/kg, followed by continuous application of Sufentanil (4 Minutes) up to 0 7 μg/kg, followed by a bolus of 20 ml of sodium chloride, followed by a bolus of 0 2 mg/kg Ethomidate.

Regime 2: Continuous application of Sufentanil (4 Minutes) up to 0.7 μg/kg, followed by continuous application of Midazolam (4 Minutes) up to 0 07 mg/kg, followed by a bolus of 20 ml of sodium chloride, followed by a bolus of 0.2 mg/kg Ethomidate.

Regime 3: Continuous application sodium chloride (8 Minutes) followed by a bolus of Midazolam 0.07 mg/kg and Sufentanil 0.7 μg/kg in a total amount of 20 ml, followed by a bolus of 0.2 mg/kg Ethomidate.

Regime 4: Continuous application of Propofol up to 2 mg/kg followed by a bolus of 20 ml of sodium chloride, followed by a bolus of Midazolam 0.07 mg/kg and Sufentanil 0.7 μg/kg in a total amount of 20 ml.

By using the Aspect B500 monitor the BIS and SEF was monitored. By using the Dräger pEEG monitor the SEF was monitored simultaneously The EEG was documented from the beginning of induction of anaesthesia up to the beginning of surgery Heart rate, blood pressure and oxygen saturation were documented.

Results: As well the BIS as the SEF changed as expected during the period of induction of anaesthesia. Before endotracheal intubation values were lower than at the beginning of induction There were high correlations between the two devices used in the study Both devices and parameters show differences between the regimes of induction of anaesthesia, showing smooth and moderate changes of EEG under regime 1, 2 and 4 Under regime 2 patients showed more often signs of thoracic rigidity, which were correlated with significant changes of the BIS but not the SEF and were followed by a temorary decrease of oxygen saturation and increase of heart rate.

Conclusions: The BIS is a very sensitive parameter for monitoring the loss of consciousness during induction of anaesthesia. There are also different changes under different regimes of induction More data are neccessary to clear the importance of the BIS in detection of complications during anaesthesia

A.137 Who or which predicts anaesthetic depth better – the bispectral index of the EEG, pupillary responses to light or anaesthesiology residents?

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Background: Estimating anesthetic depth is a daily challenge for anesthesiologists Several methods of monitoring depth have been proposed, including hemodynamic responses, esophageal contractility, and electroencephalography However, none has proved sufficiently easy and reliable for routine use. Two recently introduced anesthetic depth monitors appear to have considerable potential: the bispectral index of the electroencephalogram and the amplitude of the pupillary light reflex.[1–3] However, it is not known whether either predicts anesthetic depth better than anesthesiologists. We therefore asked whether the bispectral index or pupillary light reflex predicts movement during routine surgery better than anesthesiology residents. We further tested the hypothesis that anesthesiologists would predict movement better during isoflurane/fentanyl anesthesia than during propofol/fentanyl anesthesia.

Methods: With IRB approval, 71 patients undergoing routine urology and obstetrical surgery were anesthetized by 9 anesthesia residents in their 1st, 2nd or 3rd years of training After induction of anesthesia, (propofol, fentanyl, succinylcholine) patients were randomly assigned to propofol or isoflurane maintenance anesthesia Patients assigned to volatile anesthesia were maintained with isoflurane in 70% N_2O; additional bolus doses of fentanyl were administered as deemed necessary The others were maintained by a continuous infusion of propofol in 70% N_2O; again, additional bolus doses of fentanyl were administered as deemed necessary by the anesthesiologists based on traditional signs and clinical judgment. (The anesthesiologists were not given access to electroencephalographic or pupillary data during the study) No additional muscle relaxants were administered The anesthesiologists estimated anesthetic depth on a subjective scale from 1 to 4, where 1 = ready for extubation, 2 = shallow anesthesia, 3 = adequate anesthesia, and 4 = very deep anesthesia. The bispectral index (Aspect A-1000, Aspect medical Systems, Natick, MA), pupillary light reflex (Fairville Medical Optics, Inc , Amersham, England), heart rate, systolic blood pressure, and anesthesiologists rating were recorded every third minute by an independent observer throughout anesthesia. Patient movement was also registered by the independent observer. Statistics were computed using t-test for independent samples. Data presented as means ± SDs.

Results: Duration of surgery was 142 ± 36 minutes, time from the end of operation until extubation was 5 ± 7 minutes During the 37 isoflurane anesthetics (969, 3-minute epochs), there were 25 movement episodes, during 34 propofol anesthetics (744, 3-minute epochs), there were 15 movement episodes.

Table Mean ± SD of different indicators of anesthetic depth before movement and no-movement epochs.

	Bispectral Index	Light Reflex (mm)	Clinical Score	Systolic BP (mmHg)	Heart rate (bpm)
Isoflurane no move	45 ± 19	0 09 ± 0 06	3 2 ± 0 6	103 ± 17	64 ± 12
Isoflorane move	53 ± 17	0 11 ± 0 03	3 0 ± 0 5	104 ± 10	66 ± 11
Propofol no move	45 ± 16	0 11 ± 0 02	3 2 ± 0 6	106 ± 18	64 ± 10
Propofol move	53 ± 16*	0 11 ± 0 02	3 ± 0 7	100 ± 16	62 ± 11

*$P < 0\ 05$

Conclusion: The incidence of movement was comparable during each type of anesthesia The Bispectral Index of EEG proved the only effective predictor of movement during routine surgery and propofol anesthesia.

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A.138 Transcranial near infrared spectroscopy and EEG during cardiopulmonary bypass

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Background and Goal of the Study: Transcranial near infrared spectroscopy (NIRS) provides regional on line measurement of saturation of hemoglobin in a specific sampling of brain tissue (1). It allows therefore the non invasive evaluation of oxygen extraction of the brain parenchyma This method helps to monitor the continuous regional cerebral oxygen saturation (rSO2) (2) The EEG represents the summation of spontaneous electrical activity arising from postsnaptic potentials primarily from the superficial layers of the cerebral cortex. The rational for using an EEG is to see the changes of frequency activity and amplitude of the waves with respect to cerebral perfusion (3)

The aim of this study was to assess the changes in rS02 using NIRS and SEF using EEG together, during different stages of cardiac surgery.

Materials and Methods: The probe of the NIRS (Somanetic Corporation Troy, MI, USA) was positioned on the right side of the forehead Two channel EEG (fronto-mastoid) was recorded using Neurometrics Life Scan EEG machine The SEF was set at 95% level and EEG was continously recorded during the study. The measurements were recorded at seven times: T1· Before induction, T2: Immediately after the induction, T3. Immediately after CPB, T4: Hypothermia, T5. Rewarming, T6· Post CPB Statistical. analysis was performed by ANOVA and multiple linear regression analysis, ($p <$ 0.05) was considered as significant.

Results and Discussion: Values of rSO2 recorded were T1· 68.40 ± 7.43, T2· 72 93 ± 9 1, T3 57.86 ± 9.1 T4 57 93 ± 10 39, T5. 60 93 ± 6.29, T6: 64.93 ± 8.50. Values of SEF recorded were T1: 14 26 ± 2.5, T2· 9 6 ± 3.6, T3: 4.8 ± 3 3, T4. 3.56 ± 2.92, T5· 6 04 ± 4.35, T6 7 1 ± 3.8 There was a significant increase in rSO2 and decrease in SEF values after high dose fentanyl induction ($p < 0.05$) As soon as CPB was started there was a significant decrease in both rSO2 and SEF values caused by hemodilution ($p <$ 0 05). The first rSo2 value immediately after CPB was considered as the baseline value for the CPB period The lowest rSo2 and SEF value of the CPB was measured during deepest hypothermia which was 29°C ($p <$ 0.05) There was a positive correlation between the rSO2 and temperature when Hb and Htc values of CPB were constant ($r =$ 0 73).

Conclusion: In this clinical study noninvasive cerebral oxygen saturation recording (NIRS) indicated that high dose fentanyl induction resulted with the greatest increase in rSO2 and decrease in SEF values which may be contributed to the decrease in cerebral metabolic rate. With the Initation of the bypass and hemodilution effect the EEG and SEF value was lowered but rSo2 changed with a positively correlated way with the temperature when Hb and Htc is constant

As a result we concluded that rSO2 values of cerebral oxymeter and SEF values of EEG changed in a pozitively correlated way but rSO2 always changed earlier than the SEF in all stages of CPB and returned to the preinduction levels later than the rSO2

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A.139 Comparative study of the TOF ratio measured by the TOF guard with and without thumb repositioning

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Background and Goal of Study: In clinical anaesthesia, tactile evaluation of the muscle response evoked by a nerve stimulator is the usual method employed to assess muscular block A more sensitive method should be used to evaluate decuransation[1]. The aim of this study was to evaluate whether by applying a load of 0 5 Newton (N) to the thumb, and thereby repositioning the thumb to its starting position, altered TOF-count or TOF-ratio during a TOF-stimulation with the TOF-Guard.

Materials and Methods: With Ethic committee approval and informed consent thirteen male patients (age 18–65, ASA I&II) were included in the study A piezoelectric accelerometer on the thumb was used by the TOF-Guard (ORGANON TEKNICA NV), one thumb with and the other thumb without a load of 0.5 N Anaesthesia was induced with sufentanil (0.3 μg kg^{-1}) and propofol (2 mg.kg^{-1}) and maintained with a propofol infusion (8 mg.kg^{-1}.h^{-1}). Four and a half minutes after induction of anaesthesia both TOF-Guards were autocalibrated. Five minutes after induction of anaesthesia rocuronium (0 6 mg.kg^{-1}) was administered Patients were allowed to decuranse spontaneously and TOF-ratio was measured up to 0 9 on both TOF-Guards [2]. Comparisons within patients were done using the paired t-test (1° line) and the Wilcoxon signed-rank test (2° line) $P \leq$ 0 05 was considered statistically significant

Results: Neuromuscular data ($n = 13$) in Table 1.

Parameter	With preload minus without preload	p-value
TOF 25% mean (SD)	−2 0 (4 9)	0 17
(min) median	−1 3	0 17
TOF 50% mean (SD)	−1 5 (3 4)	0 13
(min) median	−1 0	0 18
TOF 75% mean (SD)	−0 8 (4 9)	0 55
(min) median	−0 3	0 51
TOF 90% mean (SD)	0 0 (5 3)	0 99
(min) median	0 8	0 92

Conclusion: Applying a load of 0 5 N made no difference to the TOF-ratio when measured by the TOF-Guard. Therefore it can be concluded that as long as the thumb has a free area of movement a pre-load is not necessary

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A.140 Comparative study of the TOF ratio measured by the ParaGraph *vs* the TOF guard

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Background and Goal of Study: Mechanomyography with a force transducer is used as the reference standard This method, as well as the measurement of acceleration can be used for monitoring neuromuscular blockade [1]. This study was designed to compare the TOF-count and TOF-ratio measured by the ParaGraph versus the TOF-Guard with a load of 0 5 Newton.

Materials and Methods: With Ethic committee approval and informed consent twelve male patients (age 18–65, ASA I&II) were included into the study. The ParaGraph (UTAH MEDICAL PRODUCTS INC) uses a piezoelectric sensor on the palm of the hand to measure the evoked acceleration of the thumb [2] Anaesthesia was induced with sufentanil (0 3 μg kg^{-1}) and propofol (2 mg kg^{-1}) and maintained with a propofol infusion (8 mg kg^{-1}.h^{-1}) Four and a half minutes after induction of anaesthesia TOF-Guard and ParaGraph were started synchronously. Five minutes after induction of anaesthesia rocuronium (0 6 mg.kg^{-1}) was administered Patients were allowed to decuranse spontaneously and TOF-ratio was measured up to 0 9 Comparisons within patients were done using the paired t-test (1° line) and the Wilcoxon signed-rank test (2° line). $P \leq$ 0 05 was considered statistically significant.

Results: Neuromuscular data ($n = 12$) in table 1

Parameter	TOF-Guard minus ParaGraph	p-value
TOF 25% mean (SD)	6 1 (6 9)	0 01
(min) median	6 5	0 01
TOF 50% mean (SD)	5 7 (7 0)	0 02
(min) median	5 5	0 01
TOF 75% mean (SD)	5 0 (8 0)	0 053
(min) median	4.5	0 062
TOF 90% mean (SD)	4 2 (9 1)	0 14
(min) median	4 5	0 15

Conclusion: Both the TOF-Guard and the ParaGraph can be used to determine the level of decuransation and are equal at the relevant clinically assessed end of curarisation (TOF 75% and 90%), but there use should not be interchanged

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A.141 An alternative to adductor pollicis muscle in monitoring neuromuscular function: flexor hallucis brevis muscle

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Background & Goal of Study: Neuromuscular monitorization is one of the necessary methods in neurosurgical procedures to optimize the anesthesia management. The hand is sometimes inaccessible in the operating room and another site of neuromuscular monitorization is required. For this reason, it is aimed to compare the responses of both the flexor hallucis brevis muscle and the adductor pollicis muscle to stimulation.

Methods: 11 patients (ASA physical status I–II) who were scheduled for elective neurosurgical procedures in supine position were included to the study after institutional approval and informed consent were obtained. Without premeditation anesthesia was induced with atropin 10 $\mu g\ kg^{-1}$, thiopental 5 mg kg^{-1} and fentanyl 5 $\mu g.kg^{-1}$ and maintained with a mixture of N_2O/O_2/isoflurane Neuromuscular responses were monitored by two TOF-Guards (Biometer, Denmark). One of them measured thumb acceleration and the other measured the large toe plantar acceleration. After stabilization period performed by TOF stimuli (2 Hz) in every 15 seconds with each monitor, 0.1 mg.kg^{-1} IV vecuronium (V) was administered. The onset time, the time to 25% and 75% recovery of T_1, RI, the time to 25% of TOF ratio recovery were measured. Data were analysed with Wilcoxon test; $p < 0.05$ was considered significant.

Results & Discussion: The datum received from this study are shown at the table. (H· Hand, F: Foot)

	Onset (sec)	T_1 25% (min)	T_1 75% (min)	RI (min)	TOF25% (min)
H	135 ± 37	39 9 ± 18	58 4 ± 24	18.4 ± 8	50 5 ± 22
F	155 ± 49*	40 6 ± 15	61 ± 22	20.4 ± 9	49.2 ± 21

Values are mean ± SD *p < 0 05

Besides the onset time there were no significant differences among the groups. Sopher et al (2) found similar results by electromyography.

Conclusion: We conclude that foot can be used alternatively for clinical monitoring of neuromuscular function, especially in neuroanesthesia.

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A.142 Computer-controlled infusion of non-depolarising muscle relaxants using an adaptive neural network

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The invention of modern short-acting drugs allows new forms of anesthesia. Goal of this study was to optimize muscle- relaxation by using a closed- loop-system to apply non- depolarising muscle- relaxants

First of all was to build the hardware- requirements to get reliable maesurements. We used a DATEX AS/3 monitor, which has an integrated NMT-module (NMT = Neuromuscular-transmission) For drug-infusion a GRASEBY 3500- syringe-pump was used. There was also built a software to collect data, which was set up to a laptop-pc usual in the trade.

In the first phase we collected data of 20 ASA I or II-patients undergoing general anesthesia. For induction we applied fentanyl and propofol. Propofol was used as target- controlled- infusion (TCI) at a level of among 2.0 and 3.5 μg/ml. The application of mivacurium was controlled by hand targeted at T1-ratio among 1 and 5 percent The TOF was monitored every 12 seconds

Because of variable sensibility there is no possibility to build a linear function that describes the effect of mivacurium-infusion That is the main problem of control engineering. In the past there were some efforts to solve this problem by using a rule-based fuzzy-controller. Our point of departure was to build an adaptive neural network trained by the collected data. The advantage of neural networks is the absence of fixed rules and the possibility of using the system with various drugs. The disadvantage is the "non-transparency" of the system.

The input for our system are the following measurements:

- quantity and infusion- rate of the initial bolus
- T1 = time to complete relaxation
- T2 = recovering time to a T1-ratio >0
- T1-ratio and infusion-rates of the past 2 minutes

At present the neural network is used as predictor and decision- support-system. The system is able to predict T1-ratio and offers suggestions for controlling infusion-rates to reach a prescribed T1 ratio. The possibility of automatic infusion- control is already implemented

At present a final statistical evaluation is not possible. We collect data in the same way as in the first phase The available data show clear the superiority of the system in comparison with infusion-control by hand.

The system is able to reduce the middle consumption of mivacurium about 20 percent. Trends show also a lower variation of infusion- rates and more steadyness of muscle- relaxation. In principle the system is working well and reliable Technical problems result from duration of anesthesia connected with a deterioration of measuring-conditions after 3 hours. Our attention is directed to correct this unreliability.

A.143 C7E3-modified thromboelastography predicts plasma fibrinogen concentrations in cardiac patients

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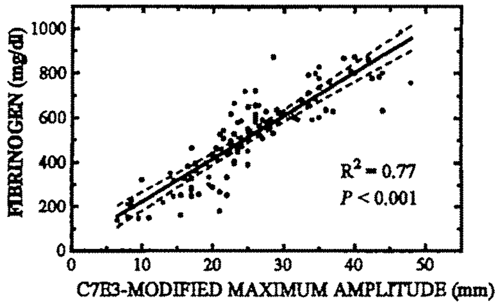
Introducton: Bleeding complications after cardiac surgery can require transfusion of blood components to maintain adequate coagulation. Rapid assessment of coagulation abnormalities is therefore essential. Thrombelastography (TEG) correlates with blood loss after cardiopulmonary bypass and can help to guide transfusion therapy (1). The maximum amplitude (MA) of TEG measures maximal clot strength, which is dependent on fibrinogen level and platelet function (2) Decrease of MA can indicate either fibrinogen deficiency or platelet dysfunction. C7E3-fab, an antibody fragment which binds to platelet glycoprotein IIb/IIIa, inhibits platelet function. Thus, c7E3-modified MA may depend mainly on fibrinogen level.

Methods: With local Ethics Committee approval and informed consent, 37 patients undergoing cardiac surgery with the use of cardiopulmonary bypass were included in this study. Blood samples (102) were obtained perioperatively and c7E3-modified MA was correlated with plasma fibrinogen level. Data were analysed by regression analysis, alpha was set at 0.05 for statistical significance.

Results: C7E3-modified MA correlated significantly with plasma fibrinogen levels (Figure).



Conclusion: Our results show that c7E3-modified MA correlates significantly with plasma fibrinogen levels. Thus, c7E3-modified-TEG could provide a rational guide in hemostatic therapy

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A.144 Cross-sectional area of the internal jugular veins: ultrasound comparison between sides and correlation with anthropometric parameters

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Background and Goal of Study: The right internal jugular vein (RIJV) is preferred for central venous, and pulmonary artery catheterization. Left internal jugular vein (LIJV) may be preferable in situations such as right neck surgery, severe right carotid stenosis or documented plaque, or inability to puncture RIJV. LIJV has been shown to have smaller cross sectional area (CSA) and distend less than the RIJV under both Tredenlenburg position and Valsalva manoeuvre(1) This study aimed to compare CSA of both internal jugular veins (IJV) before and during Valsalva manoeuvre in healthy volunteers and to correlate these findings with anthropometric parameters

Materials & Methods: Two hundred consenting adults (M/F: 107/93, 31.36 ± 15.61 years old), were prospectively enrolled, with IRB approval. Body weight, height, body mass index (BMI), sternomastoid distance, neck circumference at the level of the cricoid cartilage and xiphocostal angle were measured Luminal CSA of both IJVs were measured with 2-dimensional, multifrequential (5–10 MHz) linear surface ultrasound at the level of the cricoid cartilage. CSA was determined by planimetry during quiet breathing (control) and after 5 seconds on Valsalva manoeuvre (Valsalva), with subjects lying supine, with the head in neutral position Mann-Whitney U and Wilcoxon matched pairs tests were used as appropriate. Spearman R were calculated between each CSA measurement and the anthropometric variables.

Results & Discussion: In 125 subjects (62.5%), CSA of the RIJV was larger than that of the LIJV, in control measurements. The opposite was observed in the remaining 75 subjects (37.5%). No significant differences in anthropometric parameters were observed between these two subsets. During Valsalva manoeuvre, CSA of the RIJV was larger than the left in 147 subjects (73.5%), smaller in 51 (25.5%) and of the same size in 2 (1%). Small or non-significant correlation coefficients (Spearman R = 0.15 to 0.24) were observed between CSA of both IJVs and anthropometric parameters.

Table 1 CSA and CSA increase during Valsalva manoeuvre of both IJVs [median (lower, upper quartiles)]

	RIJV	LIJV
Control (cm^2)	1.33 (0.92, 1.78)*	1.04 (0.72, 1.49)
Valsalva (cm^2)	2.42 (1.87, 3.57)*	1.81 (1.18, 2.38)
Increase (%)	89 (49, 144)*	61 (23, 106)

* = $p < 0.05$ between sides

Conclusions: Since CSA of the right IJV is more frequently larger than CSA of the left IJV and anthropometric parameters are useless to predict CSA of internal jugular veins, right IJV should be firstly chosen, for central venous access. Moreover, since individual anatomy is unpredictable, ultrasound examination or guidance may be helpful during internal jugular veins cannulation.

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A.145 Percutaneous catheterization of the internal jugular vein: original approach

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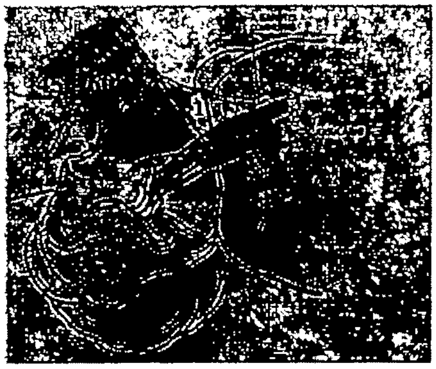
Choosing one of the techniques for finding the internal jugular vein is by all means an individual matter. However, there are differences in their successfulness and complications which can occur. We have developed a new, original approach for percutaneous puncture of the internal jugular vein using new, easily visible anatomical orienting points.

During a three-year period, percutaneous cannulation of **i.j.v.** have been performed in this way in 110 patients ranging from 22 to 84 years of age. There were 63 male and 47 female patients. All of them underwent major abdominal operations

Orientation of the puncture site is performed by inspection and by palpation. The most striking point on the front side of the neck is Adam's apple (laryngeal prominence). That is the orienting **point 1.** The mastoid process can be easily palpated behind the auricle. That is the orienting **point 2.** The clavicle and sternum junction is the orienting **point 3.** The point where the middle and the medial thirds of the clavicle unite is the orienting **point 4.** A horizontal line is drawn through the point 1. *The place where it crosses the line which connects the points 2 and 3 is the place where to puncture the internal jugular vein.* The needle is pointed towards the lateral third of the distance between the points 3 and 4, and the skin is penetrated at an angle of 45°–60° in regard to the horizontal plane (Fig.).

Catheter placement was unsuccessful in only 2 cases out of total number (110) of patients. The success percentage of 98.18% achieved. The first attempt successfulness was 86.36% (95 patients) in our series. We have cannulated the vein at the second attempt in 8.18% (9 patients), and in 3.64% (4 patients) we have not done it until the third try. The average depth of vein identification was 1.85–2.85 cm. The patients whose carotid arteries have been punctured at the third try represent the two (1.82%) unsuccessful cannulation attempts



Based on our results, we may draw a conclusion that the i.j.v. puncture technique which we established and applied to the described series of patients is simple to perform, effective and, first of all, safe for the patient.

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A.146 Factors affecting guide wire position during central venous catheter placement

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Background: At the Royal Marsden Hospital over 1000 long term tunnelled central venous catheters (CVC) are inserted annually for treatment of cancer. A Seldinger technique with radiological imaging allows early detection of guide wire malposition, avoiding reinsertion of a new catheter with attendant costs and risks. Guide wire malposition may be related to grade of operator, patient factors or approach.

Methods: 1104 consecutive infraclavicular CVC insertion records were reviewed, noting initial guide wire direction, operator grade, patient details and approach. Data were analysed using ANOVA and Fisher's exact test where appropriate. A p value < 0.05 was considered significant

Results: On initial placement 8.5% of guide wires were malpositioned. Younger age ($p < 0.0001$) and left sided approach ($p = 0.017$) were significantly associated with guidewire passage across the chest.

Results summarised in table

	Guide wire direction		
	SVC/Right atrium	Contralateral brachiocephal vein	Ipsilateral jugular vein
Numbers (%)	1010 (91.5)	45 (4.1)	49 (4.4)
Male/Female	587/423	29/16	24/25
Weight (kg. mean (range))	69.3 (25–135)	66.4 (29–102)	64.4 (26–100)
Age (yrs; median (range))	57 (10–85)	$33^{\dagger}$ (10–79)	56 (12–77)
Left sided lines (% Left lines)	182 (87.1)	$15^{\dagger}$ (7.2)	12 (5.7)
Mediastinal disease (% of med. dis)	77 (86.5)	4 (4.5)	$8^{\ddagger}$ (9)
Non-Consultant operator (%)	564 (55.8)	20 (44.4)	32 (65.3)

$^{\dagger}p < 0.05$, $^{\ddagger}p = 0.05$

Discussion: Risk groups for malposition include younger patients, or those having left sided CVCs inserted. Age related differences in vessel elasticity, and angle of approach from the brachiocephalic vein into the superior vena cava may cause the guide wire to pass across the chest. In conclusion, image intensifier control is important, particularly if there are other risk factors for central venous cannulation.

A.147 When must we stop subclavian vein cannulation attempts?

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Background & Goal of Study: Failures and complications rates of subclavian vein cannulation (SVC) are about 15 to 20% [1]. SVC with several attempts of venipuncture leads to more complications [1]. The aim of the study was to record the rates of complications and of failures according to the number of venipunctures.

Materials & Methods: Since 1993, patients requiring a SVC were included into the study. Were excluded patients with serious coagulopathy, patients in whom a SVC was already inserted or attempted. Failures and immediate complications (arterial puncture, pneumothorax, wrong position of catheter tip), the number of venipunctures per SVC and the time for SVC (between the 1rst attempt of venipuncture to the guide-wire placement) were recorded or measured. Failures and immediate complications were compared between catheterized SVC at the 1^{st}, 2^{nd}, 3^{rd} or after more than 3 attempts. Results are expressed in mean ± SD or median (with 5th and 95th) values. Statistical analysis used chi-square test ± Fisher exact test and Kruskal-wallis test. A p value < 0.05 was considered as significant

Results and Discussion: 506 patients (age = 65 ± 17 years) were included. Failures, complications and the time for SVC are shown in Table 1

Table 1

	1 VP (n = 341)	2 VP (n = 74)	3 VP (n = 32)	≥4 VP (n = 59)
Complications or failures	14 (4%)	15* (20%)	15* (47%)	43* (73%)
Failures	2 (0.6%)	2 (2.7%)	6* (19%)	24* (41%)
Complications in successful SVC	13 (3.8%)	14* (19%)	13* (41%)	32* (54%)
Art punctures	1 (0.3%)	5* (6.8%)	11* (34%)	23* (39%)
Pneumothor aces	1 (0.3%)	6* (8.1%)	2* (6.3%)	6* (10.2%)
Wrong position	11 (3%)	3 (4%)	1 (3%)	3 (5%)
Time for SVC (s)	22 (10–86)	61* (30–200)	192* (60–900)	330* (155–1200)

VP = venipuncture. * = $p < 0.05$ compared to 1 VP

When SVC were achieved in 1 venipuncture, failures and complications were rare, largely represented by wrong position of catheter tip. When more than 1 venipuncture were needed, failures and complications rates increased At the 3rd venipuncture, a failure and/or a complication were in nearly 1 case over 2.

Conclusion: After 2 failed venipunctures, the procedure for SVC has to be stopped because complications and failure rates are about 50%.

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A.148 Knowledge about pulse oximetry among residents and nurses

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Background and Goal of Study: Pulse oximetry is used increasingly in operating theatres, recovery rooms and intensive care units (1, 2) The goal of the study is to evaluate the knowledge of medical persons who are using pulse oximetry and their ability to interpret the information.

Materials and Methods: A 17 item multiple choise questionnaire (7 demographic, 10 knowledge) was developed about pulse oximetry. Interviews were completed in the same day for to prevent the respondents having the chance to revise their knowledge of pulse oximetry 12 residents in anesthesiology and 44 intensive care nurses ansuered this questionnaire. Questions were related about the theory behind the pulse oximetry, factors affecting readings, normal ranges in adult and childhood, units of measure of SpO_2 and PaO_2, relationship between SpO_2 and PaO_2, reading if cardiac arrest and respiratory arrest ensues Responses were scored against standart answers from reference texts.

Results and Discussion: Although most of the participants (98%) use pulse oximetry regularly in their daily work, 70% of the participants felt themselves enough confident about pulse oximetry Only 14% of the participants believed that they had adequate training It is considered that 86% of the participants do not understand how a pulse oximeter works. But 75% of the participants answered correctly what does pulse oximeter measure.

Conclusion: The results revealed that there is general lack of knowledge about pulse oximetry

We suggest that residency programs and nursing postgraduate programs should place more amphasis on teaching the principles of pulse oximetry and should be repeated at regular intervals.

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A.149 The advantage of preadmission anaesthesia consultation: results of a randomized controlled study

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Background: Anaesthesia consultation may take place in the department the day before the operation, or previously and be conducted well before hospitalisation In the absence of PAC, surgical operations can be delayed or cancelled through inadequate preoperative assessment and preparation The aim of this study was to evaluate the advantage of PAC compared with the usual practice, in a teaching hospital.

Methods: After approval by the Ethics Committee, 296 consenting patients scheduided for an urologic, ophtalmologic, or otorhinolaryngologic procedure, were included The trial was prospective, controlled, and randomised by random assignment of one of the following strategies: preadmission anaesthesia consultation (PAC group), or preanaesthetic visit the day before the operation (control group or PV group). The primary outcome was the length of preoperative hospitalisation. The secondary outcomes were the number of delayed operations and patient satisfaction

Table I Preoperative hospitalization duration (days)

	Group 1	Group 2	p (test t)
Population	139	144	
Urologic	2 04	2.38	0 05
Ophtalmologic	2 04	2 65	0 007
ORL	2	2 07	0.66
Total	2 04 ± 0 07	2 4 ± 0 09	0 0016

Table II Postponement of surgical procedures

	Group 1	Group 2	p
Medical postponement	2	13	<0 01
Chirurgical postponement	4	0	
total	6	13	0 17

Results: 139 patients underwent preoperative anesthetic and surgical assessment as outpatients, and 144 entered hospital on the day before surgery and underwent anaesthetic assessment as inpatients. Both groups were comparable for age, sex, surgical procedure. Table I shows the preoperative hospitalization duration. Table II shows the number of postponement of surgical procedures 85% of the group 1 patients thought that the preoperative assessment clinic put them a usefull inconvenience, and 82% thought that the preoperative assessment clinic reduced preperative anxiety.

Conclusion: PAC allows reduction of the preoperative hospitalisation period and the number of operation postponements from medical causes Early evaluation by the anesthesiologist is not a constraint for a majority of patients

A.150 Evaluation of the degree of knowledge about difficult intubation

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Goal of the Study: To evaluate the level of knowledge of anaesthetists in terms of difficult intubation (DI), anticipation and management of DI using different techniques.

Material & Methods: A survey was carried out in three representative regions in France. One hundred anaesthetists were randomly selected in each region; each of them were sent a questionnaire The first part concerned characteristics of the practitioner i,e. age, sex, years of practice, condition of exercice (university, regional hospital or private practice), number of intubations and number of DI/year. The second part assessed knowledge about DI: predictive signs, different techniques or devices, managements wether predicted or not. The last part was a survey on the actual need for intubation teaching. fibrescopic intubation, LMA, transtracheal ventilation, retrograde intubation, light stylet. After one month anaesthetists who did not reply were sent the questionnaire again. Then they were called by phone one month later if no reply has been sent.

Results: Two hundred and twenty-one questionnaires were sent back (74%)· 32% of anaesthetists worked in a university hospital, 28% in a regional hospital and 29.9% in a private practice. Five predictive signs were selected: mouth opening (93.1%), cervical mobility (92 7%), retrognathia (91.8%), Mallampati class (81%) and short neck (80 1%). In the practice, the commonest signs searched for were different than those selected: mouth opening (70%), neck mobility (63%), Mallampati class (60 1%), short neck (53 8%) and retrognathia (53 8%). The five techniques commonly used for difficult airway management were· blind nasal intubation (83.7%), LMA (81.9%), fibrescopy (53.3%), stylet (39 8%), intubation with LMA (29.4%) In case of predicted DI the techniques used are fibrescopy (43%), blind nasal intubation (27 6%) and LMA (11.8%). Awake intubation 48.3% under GA (50%) with or without muscle relaxants If DI is unpredicted the first technique used is blind nasal intubation (40 3%) then LMA (25.3%)

Discussion and Conclusion: LMA is very often used and most French anaesthetists are familar with it This study done before the publication of the expert conference on DI showed that workshops were needed for teaching purposes as well as for early detection and management of DI, since blind nasal intubation is still the most commonly used amongst anaesthetists.

A.151 Difficult intubation: evaluation of the impact of the French expert conference

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Goal of the Study: To evaluate the impact of the French expert conference (conf) on difficult intubation (DI) (1).

Material & Methods: This study was carried out in 3 regions of France, by mean of a questionnaire (quest) wich comprised 4 parts· 1) the characteristics of the anesthetist (A); 2) the predictive signs of DI; 3) the techniques used; 4) the teaching methods preferences. The quest was sent to 100 anaesthetists randomly selected in each region, 3 months before the publication of the conf (group 1, n = 300) Three months after the publication of conf, another 100 randomly selected anesthetists, in each region, were then given the same quest and added to it a survey on the impact of the conf on the daily practice (group 2, n = 300). Half of them received the abstract of the conf two weeks before (group 2b). The anaesthetists who did not receive it were considered as group 2a. Chi^2 of Pearson and Fisher's exact method were used ($p < 0.05$ significant).

Results: 90.8% of answers were received from the group 1 and 79.3% from the group 2 The groups were not different for age, sex, practice status, level of the theoritical background and level of practice. In group 2b, 80% of the anaesthetits had read the conf and in the group 2A 65.9%, but the answer concerning the predictive signs and the anticipation of the DI were not statiscally different. On the other hand, there was a better knowledge of the material and methods: combitube (p = 0.02), light-wand stylet (p = 0 003), and bullard laryngoscopes (p = 0.004) was found. The anaesthetists from group 2b claim being more aware to the predictive signs (p = 0 006)

Discussion and Conclusion: The publication of the results of the experts conference did not significantly modify the way of the daily management of DI. There is only a better knowledge of the material used It is obvious that the practical seminars and workshops are mandatory for reinforcement of the impact of this conf.

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A.152 Physical treatment of fever

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Background: Fever is by far the most common thermal perturbation In febrile patients, heart rate and metabolic stress can be substantial Consequently, fever in hospitalized patients is usually treated aggressively. When patients fail to respond adequately to anti-pyretic administration, surface cooling is a common secondary treatment Thermoregulatory theory[1], however, suggests that surface cooling in febrile patients will trigger vasoconstriction and shivering, and produce marked thermal discomfort. Furthermore, core temperature may actually *increase* to compensate for skin cooling In contrast, surface warming is likely to reduce vasoconstriction and shivering, increase thermal comfort, and may even – paradoxically – reduce core temperature. Accordingly, we tested the hypothesis that active warming is superior to active cooling in the treatment of fever.

Methods: With IRB approval we studied nine healthy male volunteers. They were given a 30 KU/kg bolus of recombinant Interleukin II, with an additional 70 KU/kg bolus two hours later. Each volunteer participated on three randomly-assigned days: 1) a single cotton blanket, 2) skin-surface cooling (15°C); or, 3) skin-surface warming (≈40°C). Thermal management continued for five hours, starting one hour after the second dose of IL-II. Core temperatures were recorded from the tympanic membrane Thermoregulatory vasoconstriction was evaluated using forearm minus fingertip, skin-temperature gradients; shivering was evaluated with indirect calorimetry and qualitatively. Integrated and peak temperatures and mean oxygen consumption during the treatment period were compared using repeated measures of ANOVA and Scheffé's F-tests Data are presented as means ± SDs, $P < 0.05$ was considered significant

Results: Peak core temperatures were 38.4 ± 0.5°C on the control day, 38.5 ± 0.4°C on the warming day and 38.1 ± 0.5°C on the cooling day Integrated core temperatures on the control day were 6.0 ± 1.6°C h, and on the warming day 6 4 ± 1 2°C·h, and on the cooling day 5.7 ± 2.2°C·h, values that did not differ significantly Mean oxygen consumption on the control day was 334 ± 45 ml/min, on the warming day 312 ± 31 ml/min, and on the cooling day 434 ± 44 ml/min Thus, mean oxygen consumption differed significantly between control and cooling day by about 30%. Duration of vasoconstriction was similar during control and cooling day, being 244 ± 85 min respectively 268 ± 65 min, whereas it was 159 ± 89 min on the warming day. Shivering was a consistent feature on the cooling day, but it was infrequent on the control day with no shivering on the warming day. Shivering on the cooling day lasted for 229 ± 35 minutes, but was only seen for 33 ± 11 minutes on the control day in three individuals. Pyrogen administration. However, it increases oxygen consumption considerably. In contrast, warming during fever virtually obliterates shivering and reduces duration of vasoconstriction significantly. Surface cooling thus appears to be a poor treatment for fever – at least in patients who are not heavily sedated or paralyzed.

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A.153 Influence of paralysis on the development of fever during isoflurane anaesthesia

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Background: Fever occurs during anesthesia in response to infectious or non-infectious etiologies. However, intraoperative fever is relatively rare considering how often pyrogenic etiologies are likely to be present, and how common fever is postoperatively. This low incidence in part results from dose-dependent inhibition of fever by general anesthesia Additionally, paralysis, may also contribute by preventing shivering. We therefore tested the hypothesis that paralysis decreases peak and integrated core temperatures after pyrogenic stimulation, during isoflurane anesthesia

Methods: With IRB approval we studied seven healthy male volunteers They were given 30 KU/kg bolus of recombinant Interleukin II, with an additional 70 KU/kg bolus 90 minutes later. Thirty minutes after the second dose of IL-2, the volunteers were randomly assigned to either 1) paralysis or 2) no muscle relaxants Anesthesia and paralysis continued for six hours. Core temperatures were recorded from the tympanic membrane Thermoregulatory vasoconstriction was evaluated using forearm minus fingertip, skin-temperature gradients, shivering was evaluated with indirect calorimetry and qualitatively. Integrated and peak temperatures and integrated heat production during anesthesia were compared using two-tailed, paired t-tests. Data are presented as means ± SDs; $P < 0.05$ was considered significant.

Results: Core temperature on the unparalyzed day reached a peak of 37.6 ± 0.9°C whereas the peak on the paralyzed day was 37 2 ± 0.6°C Integrated core temperatures on the unparalyzed day were 3.4 ± 3.4°C·h, and on the paralyzed day 2.1 ± 3 1°C·h, thus insignificantly differing by 1 3 ± 2 1°C·h Integrated heat production without muscle relaxant was 4 2 ± 0 4 kcal/kg, with paralysis 3.6 ± 0.4 kcal/kg Thus, integrated heat production differed significantly by 0 7 ± 0.3 kcal/kg over the study period. The onset of fingertip vasoconstriction was similar in both groups, being 2.1 ± 1 hours on the unparalyzed day and 2.2 ± 1.5 hours after induction of anesthesia. Shivering was a consistent feature on the unparalyzed day It started 6 ± 43 minutes after the onset of vasoconstriction and lasted 54 ± 30 minutes

Conclusion: Paralysis does not significantly reduce integrated or peak core temperatures following pyrogen administration. Vasoconstriction thus appears to be the major factor contributing to development of fever during anesthesia.

A.154 Comparative study of tympanic, bladder, oesophageal and pulmonary artery temperature measurement during major abdominal surgery

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Background: The maintenance of normothermia during major surgery is now becoming an important goal as the effects of changes in body temperature on peri-operative morbidity are increasingly recognised The most accurate method of core temperature measurement is said to be via a pulmonary artery (PA) catheter but its insertion has inherent risks and large volume transfusion may affect readings [1] In this study we have compared PA temperature measurement with other conventional sites and also with an infra-red (IR) tympanic probe in an attempt to establish an alternative acceptable reflector of core temperature.

Method: 10 patients undergoing orthotopic liver transplantation were studied. PA temperature was monitored with a Baxter thermodilution catheter and oesophageal, bladder and tympanic temperature with Mallinckrodt Mon-a-therm™ temperature probes. An IVAC Corecheck™ IR tympanic monitor was used to obtain intermittent readings from the opposite tympanic membrane. Temperature was recorded from each site at set points during surgery. Agreement between measurements was assessed by comparing mean difference from PA temperature (instrument bias) and standard deviation (SD) of differences (precision).

Results: There was good correlation between PA temperature and the four other sites. oesophagus, r = 0 97, bladder, r = 0 90, tympanic probe, r = 0 85 and tympanic IR, r = 0.96.

Mean difference (±SD) between PA temperature and oesophagus was –0 18 ± 0 2, between PA and bladder –0.15 ± 0.44, between PA and tympanic probe 0.08 ± 0.57 and between PA and tympanic IR –0 53 ± 0 25.

Conclusion: All four sites provided a close estimate of PA temperature with the oesophageal site being the most precise Tympanic IR temperature using the IVAC Corecheck™ provides an accurate, non-invasive method of temperature measurement and is an acceptable reflector of core temperature during major surgery

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A.155 Preservation of heat and humidity after 48 hours use of one hygroscopic heat and moisture exchanger

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Background & Goal of the Study: The aim of this study was to determine whether changing heat and moisture exchangers (HMEs) every 48 hours rather than 24 hours would affect their efficacy to preserve heat and moisture of expiratory gases.

Material & Methods: after randomization, 29 patients were allocated to one of the three following groups Patients in group 1 were ventilated for 24 hours with a HME (Humid-Vent Filter Light, Gibeck, Sweden) Patients

In group 2 were ventilated for 48 hours with the same HME, and patients in group 3 were ventilated for 48 hours with a heated humidifier system (HHS) (Bennet Cascade 2 humidifier). In each patient, during the inspiration phase, the following measurements were performed: peak and mean airway pressures, mean values of temperature, relative and absolute humidity of inspired gases. In each patient, measurements were performed after 24 hours and after 48 hours where appropriate.

Results & Discussion: After 24 h, patients in groups 1 and 2 had similar levels of temperature (30.1 ± 2 7 and 29 2 ± 2 3°C), relative humidity (98.3 ± 3 6 and 99.3 ± 3 4%), and absolute humidity (29.1 ± 2.1 and 29 3 ± 2.4 mg H2O/l). Using the same HME for 48 h rather than 24 h did not affect its technical performances: temperature 24 h: 29.2 ± 2.3°C, 48 h 28.7 ± 1.9°C, relative humidity 24 h: 99.3 ± 3 4%, 48 h· 99.2 ± 1.7%; absolute humidity 24 h: 29.3 ± 2 4 mg H2O/l, 48 h· 28.7 ± 3.1 mg H2O/l.

Conclusion: Changing the HME after 48 h rather than 24 h did not affect its technical performance in terms of heat and water preservation of ventilatory gases.

A.156 Effect of humidification on the incidence of adverse airway events during deepening of anaesthesia with desflurane

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Background & Goal of Study: Desflurane has a very low blood:gas solubility of 0 42, making it potentially useful in day-case anaesthesia (1). Its use has, however, been hampered by its irritant nature. Van Heerden demonstrated that adverse airway events during induction with isoflurane were reduced by humidifying the gases delivered to patients (2). We therefore investigated whether humidification affected the incidence of adverse airway events during induction with propofol and desflurane.

Materials & Methods: 60 ASA grade 1 and 2 female patients received 3MAC desflurane gradually introduced in N_2O and O_2 (2:1), following preoxygenation and induction with propofol 3 mg.kg^{-1} Gases were delivered through a Bain breathing system. Patients were randomly allocated to receive either low or high humidification using two different breathing system filters (Pall BB25 and DAR Hygrobac S, respectively) in a double blind manner. Adverse airway events (coughing and laryngospasm) were noted. Fisher's Exact Test was used for analysis

Results & Discussion: 58 patients completed the trial, with 29 in each filter group. Overall high humidity did not significantly reduce the incidence of adverse airway events compared to low humidity (10/29 and 17/29, respectively). However, 28/58 patients smoked and these were more likely to suffer adverse airway events than nonsmokers (19/28 and 8/30, respectively, $p <$ 0 05). Nonsmokers with low humidity gas were more likely to suffer adverse airway events compared to high humidity (6/13 and 2/17, respectively, $p < 0.05$). Smokers were more likely to cough than non-smokers (17/28 and 5/30, respectively, $p <$ 0 05), but were equally likely to suffer laryngospasm (6/28 and 5/30, respectively). Overall, the incidence of laryngospasm was reduced in patients receiving gas with a high humidity compared to low (2/29 and 9/29, respectively, $p <$ 0 05).

Conclusions: Anaesthetists should encourage patients to refrain from smoking prior to surgery (3). Breathing system filters with a high moisture ouput reduce the incidence of adverse airway events during deepening of anaesthesia with desflurane in non-smokers

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A.157 Failure of warmed insufflation gas to prevent hypothermia during laparoscopic hysterectomies

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Background & Goal of Study: Hypotermia is a problem in long laparoscopic operations (1). Warming of the delivered CO_2 insufflation gas may be useful (2). We tested the effectiviness of warmed CO_2 insufflation gas during laparoscopic hysterectomies (LH).

Material and Methods: 37 consenting women with permission of Ethics Committee of the hospital were randomized into heated (37°C; n = 18) and unheated (room temperature, n = 19) CO_2 insufflation groups. Tympanic (t_{tymp}) and skin (t_{skin}) temperatures were recorded preoperatively, in the beginning of anaesthesia and surgery, and every 15 minutes during operation In postanaesthesia care unit t_{tymp}, t_{skin} and shivering were measured at 15 and 75 minutes after extubation. The anaesthesia was standardized sevoflurane- O_2- air after propofol induction. All fluids were warmed.

Results and Discussion: There were no differences in the parameters measured (see Table).

Table Characteristics and temperatures (t°C) Values are 95% confidence intervals for mean

	Heated	Unheated group
Age (years)	43–49	46–50
Used CO_2 gas (l)	100 5–192 2	95 1–145 4
Duration of anaesth (min)	70–83	65–84
Δ t_{tymp} during anesth	– (1.4–0 9)	– (1 0–0 7)
Beginning of anesthesia		
t_{tymp}	36.8–37 2	37 0–37.3
t_{skin}	29 9–31.8	30 7–32 5
Beginning of operation		
t_{tymp}	36.2–36 6	36.4–36 8
t_{skin}	33 2–34 6	34 2–35 2
End of operation		
t_{tymp}	35 6–36 1	36.1–36 4
t_{skin}	33 6–34 6	32 9–34.7

Shivering between the groups did not differ postoperatively. Preanaesthetic values in t_{tymp} were reached at 90 minutes postoperatively. In some patients, the core temperature decreased below 36° C.

Conclusion: In patients undergoing LH, where the duration of anaesthesia was around 75 min, the patients did not benefit from heated gas insufflation.

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A.158 Comparison of four forced-air blankets for intraoperative cutaneous warming

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Background: Forced-air cutaneous warming is an efficient method for preventing intraoperative hypothermia [1]. Several forced-air warming systems are available today, but a study in unanaesthetized volunteers has shown that they were not equally efficient [2]. The type of the air-blanket appeared to be one of the factors contributing to the difference. The aim of this study was to compare, under clinical conditions, the efficiency of 4 different covers using one common power unit

Material and Methods: 40 adult patients ASA 1 or 2, scheduled for abdominal surgery in a supine position lasting at least 3 hours gave their informed consent to enter the study. They were intraoperatively warmed with a lower-body air b'anket covering the lower limbs. They were randomly assigned to one of four groups according to the type of blanket: Bair Hugger®, Mallinckrodt®, Thermacare®, Warmtouch®. All the blankets were attached to a power unit Bair Hugger 505 set at 43°C. The air blanket was covered with a cotton sheet if recommended by the manufacturer Core temperature (T) was monitored at the tympanic site every 15 minutes. Skin T were registered from 3 sites on the lower limbs Results (mean ± SEM) were compared using t-test and ANOVA.

Results: The four groups did not differ for age (56 ± 2 yr), weight (68 ± 2 kg), and ambient T (20.0 ± 0.1°C) The time courses of core T are shown in the figure. They were no significant differences between the groups until the third hour of anaesthesia. The highest skin T registered was 40°C.

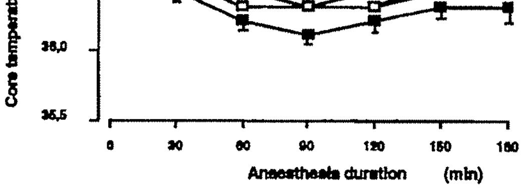

Figure Time course of core temperature during surgery in the four groups No difference between groups

Conclusion: The four forced-air warming blankets evaluated in our study had comparable efficiency under clinical conditions, a result which differs from that observed in volunteers

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A.159 Tissue thickness shift detection by a new miniature ultrasound device in anaesthetic practice

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Background and Goal of Study: A new non-invasive ultrasonic miniature device (GDM, Krautkramer GmbH & Co, Hurth, Germany) is available to measure the tissue layer thickness in circumscribed superficial tissue areas where the underlaying bone provides good backwall echos (1). This method could be helpful in anaesthetic practice to guide the fluid therapy and to detect development of tissue edema at an early stage. The superficial tissue thickness (TT) is determined by the renal and cardiac function But patient's positioning and infusion regime influence the parameter. Aim of our study was to get basic data about changes of TT under typical pre-anaesthetic conditions.

Probands, Materials, and Methods: After approval of the study design by the local ethical committee we measured the TT at forehead area in 20 male healthy volunteers (age 24–37 years, body weight 62–94 kg, normal BMI) before and 30 minutes after three procedures (P1–3): P1· change from upright to supine position P2 infusion of 10 ml/kg b w of ringer's solution after achieving a mild hypovolaemia by physical effort (average fluid loss of 508 ml) Haematocrit was evaluated before and after infusion P3: change from supine to 30° head down tilt position. Differences between the measurements were assessed by a Friedman test A $p < 0.05$ was considered significant

Results and Discussion: TT in the probands was 4 30 ± 0.12 mm (mean ± s e.m) In the upright position Procedure P1 lead to an increase of 0 11 ± 0.025 mm Rehydration after a mild hypovolaemia (P2) results in an extention of TT of 0 17 ± 0.06 mm. Mean decrease of the haematocrit was 0.02, which indicates a little overcompensation of fluid deficit. The largest augmentation of TT (0 28 ± 0 051 mm) was seen with the head down positioning (P3) These changes were statistically significant.

Conclusion: By the tested new miniature ultrasound device we could show the dimension of expected increase of TT in typically anaesthetic procedures in healthy probands, namely the change of body position and infusion therapy. This knowledge can be used in studies of volume administration.

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A.160 Tissue thickness shift detection by a new miniature ultrasound device during the perioperative period of healthy surgical patients

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Background and Goal of the Study: Assessment of patient's perioperative fluid state misses easily available and non-invasive parameters for guidance of fluid therapy Before determining hypovolaemia or overinfusion it is necessary to get basic data of the course of a new parameter in otherwise healthy patients during surgery Aim of the present study was to evaluate changes of tissue thickness (TT) with an easy to handle ultrasound device during the perioperative course of healthy surgical patients under a standardized fluid regimen.

Patients and Methods: After obtaining ethics committee approval we studied 60 ASA 1–2 patients undergoing comparable surgical procedures with no blood loss under general anaesthesia. All patients were starved for a preoperative period of more than 12 hours. After induction of anaesthesia Ringer's solution was continuously infused at a rate of 8 ml/kg b w. for the first 120 min of the operation TT of the forehead skin area was determined the evening before the operation (te), at induction (t0), followed by intervals of 30 min (t30, t60, t90, t120), and after 24 h at the next evening (t24 h) Simultaneously the haematocrit was evaluated Differences between the measurements were assessed by a Friedman test $P < 0.05$ was considered to be significant.

Results and Discussion: Starvation period (te to t0) lead to a significant decrease of mean TT from 5.03 to 4.60 mm and simultaneously the mean haematocrit increased from 36.8 to 37 9%. During the first 90 min of the procedure and standardized infusion therapy the mean TT-value significantly restituted gradually to 5.09 mm. This value kept stable until the end of the observation period (TT at t24 h = 5.05 mm). The haematocrit decreased significantly in the first 30 min to 33 7% and kept stable during the rest of the observation time The marked fluid deficiency of starvation period as well as the continuous refilling by the infusion therapy is well reflected by the evaluated data of peripheral tissue thickness. In contrast to these findings, the intravasal volume remains in a narrow range throughout the operation shown by the unchanged haematocrit.

Conclusions: The results of the present study demonstrate that perioperative changes of TT of the skin can be easily detected with the tested ultrasound device in healthy surgical patients under the test conditions These data could become a rational basis for non-invasive assessment of patient's fluid state

A.161 Anxiety does not alter gastric emptying

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Background and Goal of the Study: It has been suggested that preoperative anxiety causes a delay in gastric emptying (1, 2) However, previous investigators have not formally quantified anxiety (1), or examined only the effect of anxiety relative to a patient's predisposition to anxiety (2). The objective of this study was to examine the association between anxiety {measured using the Spielberger State Trait Anxiety Inventory (STAI) and Amsterdam Preoperative Anxiety and Information Scale (APAIS)} and gastric emptying.

Material and Methods: The STAI and APAIS scores for 16 ASA 1 or 2 patients were obtained on the morning of surgery Gastric emptying was then measured using the paracetamol absorption technique (3) Four to 10 weeks later, gastric emptying was again measured, and STAI and APAIS scores were obtained. Data were analysed using paired Students t-tests and linear regression

Results and Discussion: STAI anxiety state scores were significantly greater preoperatively than postoperatively (P = 0 004) Within patient comparison of pre- and postoperative measures of gastric emptying {area under the plasma paracetamol concentration/time curve (AUC) and peak paracetomol concentration (Cmax)} demonstrated no difference (P = 0 39 and 0 49 respectively) Linear regression demonstrated no significant association between AUC (P = 0 69) or Cmax (P = 0.48) and the anxiety component of APAIS. These findings suggest that anxiety does not influence gastric emptying. This is in contrast to previous studies (1, 2) A clinical implication of our findings is that the use of anxiolytic premedicants is unlikely to affect the residual gastric volume at induction of anaesthesia, and thus the risk of pulmonary aspiration of gastric contents.

Conclusion: Preoperative anxiety does not alter gastric emptying.

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A.162 Laparoscopic surgery of gastro-oesophageal reflux: ECG and enzymatic study

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Background & Goal of Study: Gastroesophageal reflux is an increasing indication of laparoscopic surgery [1] Specific cardiac implications were rarely reported in literature, except direct cardiac trauma from a laparoscopic instrument [2, 3]. In consequence to one case of postoperative acute myopericarditis, we analyzed perioperative ECG and postoperative myocardial enzymatic modifications following laparoscopic Toupet fundoplication

Materials and Methods: 25 patients ASA 1, scheduled to undergo gastroesophageal reflux laparoscopic surgery (Toupet fundoplication) were prospectively studied General anaesthesia was standardized with penthotal, sufentanyl, isoflurane, atracurium, and 50% N2O ST segment depression (ST > 1 mm, > 1 min, 60 ms J point) analysis was performed in peroperative period Conventional ECG and non specific (CPK, ASAT, ALAT, LDH, myoglobin) and specific (Troponin Ic, CK-MB) enzymatic analysis were measured in blood sample at arrival in postanaesthetic care unit (TO), 4 h (T4) and 24 h (T24) postoperatively Chest radiography was made at arrival in PACU. If perioperative ECG or troponin disturbances occurred with any chest pain, we prescribed also transthoracic echocardiography TTE. Demographic data were expressed as mean ± SD.

Results & Discussion: 9 women and 16 men, aged 54 ± 15 years, weighing 75 ± 10 kg, were studied. Pneumoperitoneum and hospitalization times were respectively 188 ± 55 min (90–280) and 4.0 ± 0 9 days (2–10). Any peroperative ST segment depression was noted, including during hypotensive (BP ≤ 80 mmHg; 3/25 patients) or hypertensive episods (BP ≥ 160 mmHg, 1/25) One case of peroperative subcutaneous emphysema occurred without ST disturbance. Except one case of conversion into laparomy, any peroperative surgical complication was reported In postoperative period, we found 5 patients with negative T in ECG, without ST segment depression but whose 2 presented vagal bradycardial episod and 2 atypical chest pain, without cardiac enzymatic increase and abnormality of segmental ventricular motion or gazeous in pericardium in TTE. Troponin Ic and CK-MB were not increased postoperatively. Significant increase of CPK and LDH occurred in one patient with negative T in ECG at T0 without TEE modification and morbidity. On the other hand, we found 7/25 patients with significant myoglobin increase. Among of them, one presented elevated myoglobin from TO to T24, with a transient dizziness in PACU, and experienced a diaphragmatic rupture in postoperative day 7 Transaminase concentrations were increased (2-fold normal TGO-TGP values) in 12/25 patients. Among these 12 patients, 5 experienced transaminases elevation up 5–10 fold normal values, without postoperative liver failure or cholestasis, but correlated with left hepatic artery ligature.

Conclusion: In this preliminary study of 25 laparoscopic surgical repair of gastro-oesophageal reflux, we did not find peroperative ST and postoperative ECG modification or specific myocardial troponin Ic disturbances. Unexpectedly, incidence of hepatic cytolysis was frequent (48%), and not reported in literature

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A.163 Effect of cricoid pressure on gastro-oesophageal reflux

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Background and Goal of Study: Cricoid pressure applied at a force of 44 N completely occludes the upper oesophagus to prevent regurgitation of stomach contents into the pharynx, even in the presence of gastro-oesophageal reflux (1). Cricoid pressure has recently been shown to decrease lower oesophageal sphincter tone (2). This decrease was present even at cricoid pressure of 20 N. This finding has important clinical implications The aim of this study is to investigate whether cricoid pressure promotes gastro-oesophageal reflux.

Methods: 15 healthy volunteers were studied after fasting for more than 4 hours Following local anaesthesia to the nostril, a fine bore oesophageal pH catheter was advanced into the stomach and then withdrawn 4–5 cm above the gastro-oesophageal junction. Cricoid pressure was applied for 60 seconds by resting a padded yoke weighing 4.5 kg on the cricoid. Oesophageal pH was recorded with a Digitrapper MD and analysed with Gastrosoft software (Synectics Medical Limited). Recordings were commenced one minute prior to application of cricoid pressure and continued for a minute after the manoeuvre had been completed. A reflux episode was defined as a fall in oesophageal pH to less than 4 (3).

Results and Discussion: The median (range) resting stomach and oesophageal pH were 1 2 (0 8–1.5) and 6.7 (6.0–6.9) respectively In no subject did the oesophageal pH fall below 4 during application of cricoid pressure One subject, after cricoid pressure was relieved, had a swallow related reflux spike lasting 6 seconds. Assuming a binomial distribution, the probability of not detecting an episode of reflux, if the true incidence of reflux during cricoid pressure is 20% or more, is 0.035.

Conclusion: Cricoid pressure is not associated with a significant risk of gastro-oesophageal reflux in awake starved volunteers

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A.164 Capnography monitoring in non-intubated patients during recovery from anaesthesia

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Background & Goal of the Study: During the last decade, pulse oximetry and capnography have become standard monitoring during anaesthesia. However, capnography is not employed during recovery from anaesthesia, in spite of being theoretically useful, due to the lack of a reliable commercial system for non-intubated patients. The aim of the study is to evaluate continuous capnography monitoring in non-intubated patients in the postanaesthesia care unit (PACU), employing an easy and simple system.

Material & Methods: After informed consent and with a prospective design, 32 ASA I–III patients who underwent abdominal surgery have been studied during recovery from general anaesthesia. Cardiac rate, blood pressure and SpO2 were monitored in all patients. If SpO2 < 95%, the patient was given supplementary oxygen via face mask (FiO2 = 0.4). Continuous capnography monitoring was also established by direct introduction of the sampling tube luer terminal of an infrared monitoring device (Kontron) into the nostril All the parameters and the presence and shape of the capnogram curve were noted every 5 minutes during the first 15 minutes, every 15 minutes during the following 120 minutes and after, every 30 minutes until discharge from the PACU. Arterial gases and capnogram printing were performed simultaneously 30 minutes after the patient arrival at the PACU Apnoea, hypoventilation, and sampling tube obstruction or mobilisation episodes were noted. Data are presented as mean ± standard deviation and have been analysed using the T Student test, a simple correlation analysis, and tests of bias and precision

Results: The duration of monitoring ranged from 130 to 480 minutes (mean 211.71 ± 83 03). There were not statistically significant differences when mean age and the other studied parameters, including PaCO2 and ETCO2 during the first 120 minutes, were compared. Capnogram was defined by the shape of the curve at the moment of the measurement in 67% of all measurements (n = 320) and there were not statistically significant differences between the group that required supplementary oxygen and the group that didn't. There was significant direct correlation (P < 0 01) between ETCO2 and PaCO2 (r = 0.78, bias = 4.8 and precision = 3 34) 13 false apnoea episodes, 8 cases of hypoventilation (ETCO2 > 40 mmHg and/or RR < 8) during the first 15 minutes, and 7 cases more including the following 120 minutes, were detected by audible alarms. Of these hypoventilation episodes, 5 patients also developed hypoxemia (SpO2 < 95%), always after the hypoventilation episode. Seven cases of the luer terminal and/or sampling tube mobilisation and none of obstruction were reported All cases of hypoventilation and three cases of hypoxemia were resolved by stimulating the patient. No patient was disturbed or injured by the introduction of the luer terminal into the nostril

Conclusions: These results about capnography monitoring by direct introduction of the sampling tube luer terminal into the nostril show that. 1) it can be considered an accurate method for capnography monitoring in non-intubated patients, 2) it allows us to detect hypoventilation and apnoea, 3) it neither disturbs nor hurts the patient, it is not easily moveable or obstructed, and 4) it is suitable for long lasting monitoring

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A.165 Evaluation of a new colorimetric $ETCO_2$-detector (Colibri) for confirmation of adequate lung ventilation

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Background and Goal of Study: Capnographic or colorimetric determination of end-tidal CO_2 ($ETCO_2$) is one of the most reliable methods for confirmation of adequate lung ventilation after intubation (1). A new colorimetric device (Colibri, Icor, Bromma, Sweden) overcomes major shortcomings compared to earlier devices (2): It has a faster response to $ETCO_2$-changes, a longer shelf life and it is available in two different sizes (adults and children) The aim of our study was to determine the utility of the Colibri for confirming endotracheal tube position after intubation in children as well as in adults, and to evaluate the device as a monitor during mechanical ventilation

Materials and Methods: Seventeen children (age 2.8 ± 3.7 years, weight 14 ± 15 kg, group 1) and 36 adults (age 58 ± 15 years, weight 74 ± 13 kg, group 2) were included into the study Immediately after intubation the device was attached between endotracheal tube (ETT) and ventilation bag and a first reading was obtained by the investigator. Simultaneously, ETT position was determined by the anaesthesiologist using clinical methods and capnography Any color change from blue ($ETCO_2 < 4$ mmHg) to dark green ($ETCO_2$ 4–10 mmHg), light green ($ETCO_2$ 10–30 mmHg) or yellow ($ETCO_2 > 30$ mmHg) was considered to indicate endotracheal tube placement. The device was left in its place until end of anaesthesia Readings were obtained regularly and compared to capnographic measurements.

Results: All three esophageal tube misplacements in group 2 and one tube dislocation immediately after endotracheal intubation in group 1 were promptly detected by using the Colibri. The devices worked sufficiently during anaesthesia in all but one case (device became wet) In all patients colorimetric readings showed a very good agreement with capnographic measurements.

Conclusions: Colorimetric $ETCO_2$ monitoring using the Colibri is a safe, rapid and simple method for determining endotracheal tube position after intubation in hemodynamically stable patients The Colibri might be used as indicator of $ETCO_2$ during mechanical ventilation when capnography is not available.

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A.166 Are colorimetric carbon dioxide detectors reliable over longer periods?

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Background and Goal of Study: After endotracheal intubation, CO2-detection in exhaled air is important for verifying proper tube placement Recently, disposable colorimetric CO2 detectors have been developed for this purpose Our objective was to investigate whether these detectors are suitable for continuous use over longer periods in endotracheally intubated ventilated patients

Materials and Methods: We studied two colorimetric detectors, the Easycap (Nellcor, USA) and the Colibri CapnoFlex (ICOR, Sweden), prospectively in 20 ventilator-treated intensive care patients (in ten patients the Easycap and in the other ten the Colibri in random order) for a period of 24 hours and compared the detectors every other hour with a calibrated in-stream capnometer (HP, USA) and intermittently with arterial PCO2 from simultaneously drawn arterial blood samples The color of the detector membrane was read by two independent observers Since pilot-tests showed that the function of the detectors was sensitive to humidity, the detectors were attached between an HME (Humi-Vent Filter Light, Gibeck, Sweden) and the Y-piece The CO2-cuvette was placed between the colorimetric detector and the Y-piece

Results and Discussion: One detector in the Easycap group deteriorated after 14 hours, while the other detectors in both groups functioned well over the 24 hours test period The Colibri detects CO2 semiquantitatively in the 0–4% range, and the Easycap in the 0–5% range. Thus, the color shift is maximal at 4 and 5%, respectively This was shown in this study, where the Colibri and the Easycap indicated >4 and >5% end-tidal CO2, respectively, compared with the capnometer which showed 2 7–6 3% (range) when the Colibri was used and 3 6–6.8% when Easycap was used PaCO2 was 3.9–7 6 kPa Both detectors indicated 0% CO2 during inspiration The color change was more difficult to detect with the Easycap than with the Colibri. The Colibri was easier to attach to the endotracheal tube than the angled Easycap but the side-wing Colibri is designed to give an air-leak (0.2–1.5 l/min in our test), which makes it less suitable for prolonged use during inhalation anesthesia

Conclusions: Nineteen of twenty detectors were reliable for end-tidal CO2 detection in periods up to 24 hours. However, they were inexact in the normal end-tidal CO2 range. The Colibri has a better design regarding the reading of the color change, the attachment to the endotracheal tube, a lower dead space and a lighter weight

A.167 Ethanol absorption during operative hysteroscopy

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Fluid absorption is a well known phenomena during operative fluid irrigation, but this has not often been described in patients undergoing operative hysteroscopy. The aim of this study was to measure absorpton of alcohol in comparison to other parameters during fluid irrigation.

110 patients were monitored during operative hysteroscopy The irrigation fluid was a Purisole™ solution (Fresenius) containing 2% ethanol General anesthesia was induced with propofol, fentanyl and vecuronium and maintained with isoflurane and nitrous oxide. From the normoventilated Patient endexspiratory alcohol concentrations were measured using an Alkomat 3010™ (Biotest, Dreleich) every 2 minutes. Sodium, haemoglobin and haemodynamic parameters including Cvp were monitored during anesthesia

Results: Operative procedures with fluid irrigation is usually monitored by using measurments of Na, Hb and Cvp Unfortunately these parameters tend to show a wide spread. The information on fluid absorption seems to be improved by nearly online alcohol tracing method In 47 patients no alcohol absorption was detected 45 Patients showed minimal absorption of irrigation fluid (alc endex <0 2‰). In 8 patients we measured endexspiratory alcohol concentrations between 0 2‰–0 4‰ and 10 Patients showed even higher value.

Our results suggest that endexspiratory alcohol measurement could prove to be a fast and save technique to detect fluid overload in patients undergoing operative hysteroscopy

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A.168 Effects of rapid blood administration on arterial blood gases continuously monitored

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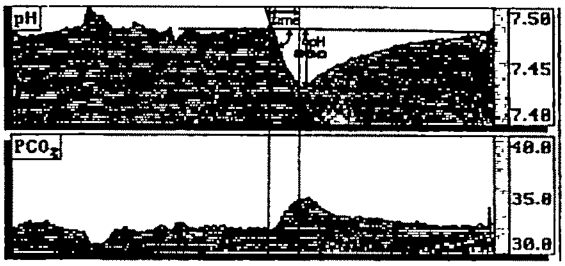
During blood transfusion, the low pH of the citrate preservative and the acid accumulation by red cell metabolism may lead to acid-base alterations, usually of transient character. These effects can hardly be detected without a continuous blood gas monitoring system, if administration is rapid For this purpose, this study involves the use of an intra-arterial fiber-optic sensor for continuous blood gas monitoring, based on fluorescent technology [PARATREND 7 (P7) Pfizer Biomedical Sensors], which has been found accurate and reliable at least for PCO_2 and pH

Material & Methods: After protocol approval, patients with preoperative adequate renal function and already monitored with P7 intraoperatively were evaluated for inclusion as follows 1) absence of any respiratory and acid-base disorder 2) rapid blood transfusion not for cardiac output improvement Twelve patients (age 68 2 ± 9.1, ASA I–III were finally included (mainly elective abdominal aortic surgery and radical cystectomies). P7 sensor was introduced through a 20 G radial artery catheter and packed red cells in CPDA-1 were transfused in all cases Blood administration began when acid-base steady state was apparent and under conditions of relative hemodynamic stability. Ventilation was kept unchanged during observation Graphs were processed after planimetry

Results: Transfused blood had a weight of 622.9 ± 285.8 g (mean ± SD), it was stored for 15 1 ± 4 4 days and it was given at a rate of 72 0 ± 9 5 g/min Arterial pH decreased from 7 447 ± 0 023 to 7 385 ± 0 034 ($p < 0\ 001$) while PCO_2 increased from 32.3 ± 1 3 to 36 3 ± 1 8 ($p < 0\ 001$) ΔpH (−0.062 ± 0 024) and ΔPCO_2 (3 9 ± 1.0) showed significant correlation to the weight of transfused blood (r = 0 889 & r = 0.586 respectively) ΔpH showed significant correlation also to the product (weight × days of storage) (r = 0.675). The tangent of pH alteration had a slope of −1.15 ± 0 4 and showed positive but not significant correlation to both the rate and the days of storage (r = 0 518 & r = 0 485) Areas "above" the curve (AAC) for pH and "under" the curve (AUC) for PCO_2 (fig) showed highly significant correlations to the product (weight × days of storage) (r = 0 910 & r = 0.786) Alterations of PO_2, although indicating decreased PAO_2 (in the beginning of the transfusion) and improved ventilation/perfusion ratio (later), where not significant



Discussion: During rapid blood transfusion, although acidosis is mainly of metabolic character, a "coca-cola like effect" is also present Proton load is related to the amount and the storage of blood administered Rapidity of the produced effects is also depending on the rate of infusion Alterations are difficult to detect without a powerful monitoring system The above information may applications in the management of recipients of blood

A.169 Prediction of plasma fibrinogen concentration with native and activated thromboelastography

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Introduction: Thrombelastography (TEG) is a global assessment of hemostatic function, documenting the interaction of platelets with the protein coagulation cascade from the time of the initial fibrin formation, through platelet aggregation, clot strengthening and fibrin cross linkage to eventual clot lysis. The maximum amplitude (MA) of a TEG is dependent upon fibrinogen level and platelet function (1). Recent studies showed a good correlation of plasma fibrinogen level and MA when platelet function is inhibited by c7E3, an antibody fragment which binds to platelet glycoprotein IIb/IIIa (2) As the MA varies with different coagulation activators, such as celite or tissue factor, the correlation of plasma fibrinogen levels with c7E3-modified MA may also vary. Accordingly, we compared native, celite-activated, and tissue factor-activated c7E3-modified MA and plasma fibrinogen levels

Methods: With local Ethics Committee approval, citrated blood samples (20) were obtained from patients, who undergoing elective surgery. c7E3-modified MA was measured in recalcified blood without activation and with activation by celite and tissue factor. Linear regression analysis was performed to determine the correlation between plasma fibrinogen levels and c7E3-modified MA.

Results: Correlation between c7E3-modified MA and plasma fibrinogen levels was higher in activated measurements. Celite-activated measurements correlated better with plasma fibrinogen levels than tissue factor-activated measurements (Table)

Table Correlation of plasma fibrinogen levels and Maximum Amplitude

MA	Adjusted R^2	P-level
Native TEG	0.56	<0.005
Tissue factor TEG	0.69	<0.001
Celite TEG	0.76	<0.001

Conclusion: c7E3-modified MA varies with different coagulation activators. Celite-activated c7E3-modified MA correlates better with plasma fibrinogen levels, than native and tissue-factor-activated c7E3-modified MA. Thus, celite-activated c7E3-modified-TEG may provide a rational guide in transfusion therapy.

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A.170 Thromboelastographic coagulation changes after 6% hetastarch administration for the treatment of perioperative hypovolaemia

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Background: Currently used hetastarch (HS) solutions can interfere with coagulation. Whether this translates into clinical bleeding is debatable, yet the product label recommends limiting the dose to 20 ml/kg/24 hrs. Standard coagulation assays are poor predictors of coagulopathic bleeding, whereas thromboelastography (TEG) has proven more clinically useful[1]. Thus far, data on the effects of hetastarch on perioperative coagulation have not included TEG changes. Coagulation factor defects result in prolongation of both R and K times with a reduced maximum amplitude (MA) and α-angle, whilst isolated MA and α-angle reduction reflects platelet dysfunction. In contrast, a short R time with an increase MA and α-angle denotes hypercoagulability.

Methods: Following IRB approval and written consent, patients undergoing general surgical, urological and orthopedic procedures with anticipated blood loss of >500 ml entered a protocol to receive 6% hetastarch and packed cells if Hct < 0.25, to treat perioperative hypovolemia. A maintenance fluid of 5 ml/kg/hr lactated Ringers solution was infused. Native blood for paired TEG tracings was drawn on induction (pre) and at skin closure (post). Prior to closure, an objective assessment of clinical oozing was noted

Results: Twenty one patients were enrolled. The volume of colloid infused was 19 ± 3 ml/kg (mean ± SD), 8/21 patients received >20 ml/kg. Estimated blood loss was 608 ± 133 ml. No patients required FFP or PL; six patients received 2–4 units of RBC. There was no clinical oozing at the surgical site and no overall increase in hypocoagulable traces; 10/21 patients were hypercoagulable preoperatively. This is reduced to 8/21 postoperatively. With >20 ml/kg HS traces tended to become normal (Table). The pre operative R, K, MA are 15.7 ± 2.5, 5 ± 1, 66.4 ± 2.9 and post operative R, K and MA are 12.8 ± 2.5, 6.4 ± 0.9, and 58.4 ± 3.4 respectively (mean ± sd). Normal range: {R 19–28, K. 8–13; MA 48–60}. There were no significant differences between any pre and post operative parameters.

	Vol of 6% HS	Type of TEG tracing		
		Normal	Hypocoag	Hpercoag
Preop-op	<20 ml/kg	5/21	1/21	7/21
	>ml/kg	3/21	2/21	3/21
Postp-op	<20 ml/kg	4/21	2/21	7/21
	>20 ml/kg	6/21	1/21	1/21

Conclusions: The volumes of 6% HS used in this study had minimal overall impact on TEG parameters and were not associated with clinical evidence of bleeding, even when exceeding the product label recommendation of <20 ml/kg/24 hours. There is a high incidence of preoperative hypercoagulability among patients presenting for elective, major surgery. This number is reduced after perioperative administration of HS. Further study is needed to show if HS can reduce postoperative hypercoagulability.

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CIRCULATION

A.171 Clinical implications of portopulmonary hypertension in liver transplant patients

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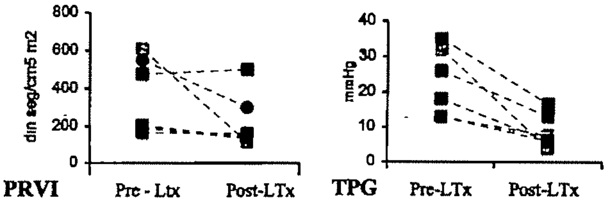
Background: The presence of Portopulmonary Hypertension (PPH) in patients with advanced liver disease often delay in diagnostic process because of symptoms initially are subtle. The perioperative risk of patient with PPH submitted to liver transplant (Ltx) must be recognised. On the other hand, the role of Ltx on PPH remains uncertain.

Aim: To investigate the incidence, clinical characteristics, and the impact of LTx in patients with PPH

Patients and Methods: Twelve of 499 patients (2.4%) submitted to LTx (between 1989 and 1996) fulfilled diagnostic criteria for PPH: elevated mean pulmonary artery pressure (MPAP) (>25 mmHg) and transpulmonary gradient (TPG) (>12 mmHg) with normal pulmonary wedge pressure (PWP), in absence of other cause of secondary pulmonary hypertension. Haemodynamic data were obtained after induction anaesthesia. The clinical history, laboratory data, pulmonary function test of these patients (PPH-Group) were recorded and compared to those of matched patients submitted to Ltx without PPH (Control-Group, n = 40). In 6 patients with PPH, pulmonary haemodynamic follow-up was performed between 18–24 months after LTx. Actuarial survival was also recorded. All data are presented as mean ± SEM. Statistical analysis was performed using analysis of variance (ANOVA) with unpaired-*t*-test

Results: PPH patients showed abnormal, but not significantly higher, alveolar-arterial O_2 gradient (24 ± 8 *vs* 17 ± 5 mmHg, $p = 0.17$), and lower CO diffusing capacity (DLCO) (68 ± 9 *vs* 83 ± 10% pred, $p < 0.05$) than CG. Patients with PPH have an increased cardiac index (CI) (5.2 ± 1.4 *vs* 4.5 ± 1.2 L/min/m², $p < 0.05$), MPAP (34 ± 11 *vs* 17 ± 5, $p < 0.05$), PVRI (398 ± 60 *vs* 135 ± 45 dynes.s.cm^{-5}.m^{-2}, $p < 0.05$), and TPG (26 ± 8 *vs* 6 ± 4 mmHg, $p < 0.05$) when compared to CG. All of them responded to vasodilator drugs decreasing PVRI 20% at least from baseline value. The six PPH patients evaluated after Ltx showed a decrease on MPAP, TPG, PVRI and CI. At 5-yr after Ltx, actuarial survival in PPH patient was 66% while it was 79% in No-PPH patients.



Conclusions: The prevalence of PPH among Ltx candidates is about 2.4%. DLCO should be a useful marker of PPH. In this group of patients with PPH, improvement of pulmonary haemodynamics was observed after LTx.

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A.172 Mixed venous oxygen saturation: evolution and correlations during liver transplantation

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Background and Goal of Study: Surgery of liver transplantation (LT) developes haemodynamic changes decreasing cardiac output (CO) after venous clamping to exclude the liver. Perioperative monitoring should give information about cardiovascular system and tissue oxygenation. Fiberoptic catheter in pulmonary artery can measure CO and mixed venous oxygen saturation (SvO_2). SvO_2 changes are conditioned with variations in: CO, hemoglobin (Hb), oxygen arterial saturation (SaO_2) and oxygen uptake (VO_2)(1, 2). The aim of this study was to determine SvO_2 evolution and its correlation with their determinants and to evaluate the utility of SvO_2 monitoring during LT.

Material and Methods: Prospective study of 45 patients undergoing LT with piggy-back technique. All patients were managed according to the LT protocol of our institution with respect to anaesthesia, monitoring and transfusion. A fiberoptic catheter (Opticath ®P711, Abbott) in pulmonary artery for continuous SvO_2 monitoring was placed. Measured parameters: cardiac index (CI), VO_2, Hb, SaO_2 and SvO_2. Study phases: T1: before surgery, T2: in hepatectomy phase; T3: anhepatic phase; T4: 5′ after unclamping; T5: neohepatic phase. Data were analysed by ANOVA test ($p < 0.05$) and Pearson lineal correlation coeficient ($p < 0.05$).

Results: Expressed as mean ± SD are showed in table below.

Parameter	T1	T2	T3	T4	T5
SvO_2 (%)	85 82 ± 5 0	85 85 ± 6 4	86 48 ± 7 1	89 79 ± 3 7	87 18 ± 4 0
CI (l min m^2)	4 96 ± 1 4	5 19 ± 1.2	3 89 ± 1 0	6 38 ± 1 4	5 63 ± 1 1
VO_2 (ml/min)	199 ± 58	186 ± 50	152 ± 51	210 ± 56	213 ± 52
Hb (gr 1)	9 85 ± 1 7	9 51 ± 1 6	9 58 ± 1 6	9 30 ± 1 5	9 30 ± 1 3

SvO_2 and CI show a direct correlation in all the study phases (T1 r = 0 52, p = 0 000, T2 r = 0 58, p = 0 000, T3· r = 0 61, p = 0.000; T4 r = 0 45, p = 0 002, T5 r = 0 36, p = 0.016). SvO_2 and VO_2 have an indirect correlation in T2 (r = –0.55, p = 0 000), T3 (r = –0.44, p = 0 004), T4 (r = –0 43, p = 0 003) and T5 (r = –0.43, p = 0.003) No correlation between SvO_2 and Hb levels

Conclusions: SvO_2 is maintained high in all the study phases, including anhepatic phase with a CI decreased (27%) by inferior venous cava partial clamping A decreased VO_2, a stable Hb and SaO_2 without changes, contribute to maintain the values of SvO_2 after clamping A direct correlation is found between SvO_2 and CI in our patients Changes in SvO_2 are explained particularly by changes in CI. SvO_2 is useful as indicator of haemodynamic state in LT

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A.173 Endoluminal laser-Doppler measurements of jejunal mucosal perfusion in patients undergoing liver transplantation

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Background: Patients undergoing liver transplantation are at risk for developing the multiple organ dysfunction syndrome (MODS) *(1)*. A decreased gastro-intestinal mucosal perfusion has been suggested of pathogenic relevance for the development of MODS *(2)* The aim of this study was to investigate the use of endoluminal laser-Doppler flowmetry for determination of jejunal mucosal perfusion during liver transplantation *(3)*.

Materials and Methods: An endoluminal laser-Doppler catheter was positioned with the tip in the jejunum for continuous measurements of jejunal mucosal perfusion in 10 patients undergoing liver transplantation Central hemodynamic parameters were registered at the end of the dissection phase, at the end of the anhepatic phase, during reperfusion and at the end of surgery.

Results and Discussion: The anhepatic phase was associated with a progressive decrease in jejunal mucosal perfusion and at the end of the anhepatic phase the jejunal mucosal perfusion was reduced to (median [25th/75th]) 49 (40/65)% (p < 0.01) of the dissection phase value At the end of surgery the jejunal mucosal perfusion had increased to 134 (103/158)% (p < 0 01) of the dissection phase jejunal perfusion. The jejunal mucosal perfusion correlated significantly with cardiac index, systemic vascular resistance index and mean arterial pressure However, the pronounced reduction in jejunal mucosal perfusion during the anhepatic phase was out of proportion to the considerable smaller changes in cardiac index and SVR index This indicate that laser-Doppler measurements of gastro-intestinal mucosal perfusion may provide additional information about the gastro-intestinal perfusion, which cannot be estimated from central hemodynamic parameters

Conclusions: Liver transplantation is associated with a decrease in jejunal mucosal perfusion during the anhepatic phase The endoluminal laser-Doppler technique was found to be easily applicable for continuous monitoring of gastro-intestinal perfusion and the technique could prove valuable to detect gastro-intestinal hypoperfusion in patients undergoing liver transplantation.

Acknowledgements: Center for Gastroenterological Research, Goteborg University and The Goteborg Medical Society

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A.174 Xanthine oxidase is directly associated with liver ischaemia-reperfusion-induced remote myocardial dysfunction

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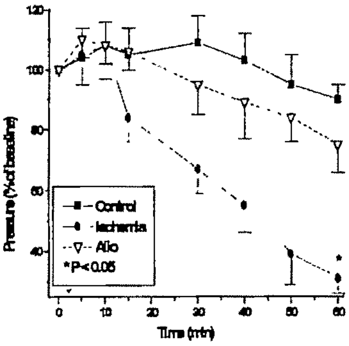
Background and Goals: We previously demonstrated the existence of a direct linkage between cardiac dysfunc-tion and post-ischemia reperfusion in a different organ (Ref) We hypothesized that xanthine oxidase (XO) and generated reactive oxygen species (ROS) are res-ponsible for such damage The present study aimed at confirming this assertion

Materials and Methods: Male Wistar rat livers were isolated and perfused with oxy-genated (37°C) Krebs-Henseleit solution (KH) After 30′ stabilization, livers were either perfused (Control, n = 6), made globally ischemic (Ischemia, n = 6), or made ischemic after being treated with XO oxidoreductase inhibitor allopurinol (Allo, n = 6) for 2 h Paced hearts from other rats were meanwhile isolated and perfused with KH via the ascending aorta (80 mm Hg, modified Langendorff preparation) The 2-h period was followed by a 15′ liver + heart reperfusion phase in which the hepatic effluent was directed into the Langendorff prep The liver was then disconnected and the only heart continued to recirculate alone with the accumulated KH for 45′ more

Results and Discussion: Left ventricular developed pressure (LVDP) in the Ischemia group decreased significantly, measuring ~35% of baseline values at 60′ of reperfusion (fig) Both myocardial velocity of contraction and relaxation (±dP/dt_{max}) decreased by a similar magnitude, as did the coronary flow All parameters remained statistically unchanged in the Controls or Allo groups of hearts. XO activity in the Allo group perfusate was as low as in the Controls but thousands of times higher than in the Ischemia perfusate The low circulating XO activity following the administration of Allo coincided with the absence of remote cardiac dysfunction



Conclusions: XO is directly associated with remote cardiac dysfunction during the period of post-ischemia reperfusion and Allo treatment proved such linkage The precise mechanism(s) by which XO and ROS can alter remote organ homeostasis await further investigation

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A.175 Effects of positive end-expiratory pressure on indices of left ventricular diastolic function during laparoscopy

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Background & Goal: CO2 pneumoperitoneum (PN) induces well-known changes in the cardiopulmonary system In presence of hypoxemia, it is sometimes necessary to apply a positive end expiratory pressure (PEEP) to improve arterial oxygenation However, the hemodynamic effect of the peep may worsen the left ventricular diastolic function (LVDF) which is already decreased by PN (1) The aim of this study was to examine the effect of PEEP on indices of LVDF obtained by transesophageal pulse Doppler echocardiography during laparoscopy

Methods: General anaesthesia (propofol, sufentanil) was administered in 10 ASA I–II informed patients scheduled for laparoscopic cholecystectomy Peak velocities of early (E cm/s) and late filling wave (A cm/s) of the transmitral blood flow were measured They were first measured after induction of general anaesthesia with the application of 5 and 10 cm H_2O PEEP, and secondly after PN was raised to 11 mmHg and with the application of 5 and 10 cm H_2O PEEP The E/A ratio and the deceleration time (DT· ms) were calculated as indexes of the LVDF Heart rate (HR beat/min) and blood pressure (BP mmHg) were recorded at the same time

Results and Discussion:

	PN 0 mmHg	PEEP 5 cmH_2O	PEEP 10 cmH_2O	PN 11 mmHg	PN + PEEP 5 cmH_2O	PN + PEEP 10 cmH_2O
BP	78 ± 9	77 ± 10	74 ± 14	97 ± 13*	103 ± 13	106 ± 12
HR	69 ± 11	67 ± 9	68 ± 9	62 ± 8	63 ± 10	64 ± 9
E	59 ± 14	47 ± 11°	44 ± 12°	44 ± 14*	42 ± 12	42 ± 10
A	43 ± 8	41 ± 8	38 ± 8	46 ± 13	46 ± 11	49 ± 10
E/A	1.4 ± 0.5	1.2 ± 0.4#	1.2 ± 0.3#	1 ± 0.5*	1 ± 0.4	0.9 ± 0.3
DT	0.14 ± 0.02	0.16 ± 0.03	0.16 ± 0.05	0.15 ± 0.03	0.15 ± 0.03	0.15 ± 0.05

* PN ANOVA $p < 0.05$ °PEEP ANOVA $p < 0.05$ #PEEP ANOVA $p = 0.057$

After Peep alone and after CO_2 insufflation without PEEP E wave decreased significantly while it does not decrease further significantly when PEEP was applied during the PN. A wave increased after PN but did not change with PEEP. E/A decreased significantly with PN and less significantly ($p = 0.057$) with PEEP alone. There was no changes in DT and HR neither with PN or PEEP. BP was increased after PN but not with PEEP.

Conclusions: These results suggest that LVDF might be reduced as a consequence of a PEEP application and as a consequence of PN. But the effect of PEEP seems to be less important in presence of a PN and does not lead to further significant decrease in E/A ratio.

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A.176 Haemodynamic and catecholamine responses to a rapid increase in sevoflurane or isoflurane concentration

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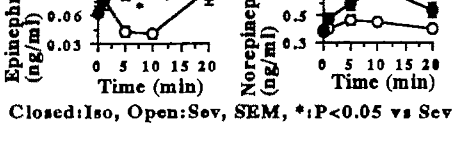
Background and Goal of Study: That the effects on sympathetic and parasympathetic nervous system are different between sevoflurane (Sev) and isoflurane (Iso) or not is still controversial. Plasma epinephrine (Ep) and norepinephrine (NEp) concentrations were reported to increase when inhaled Iso concentration was rapidly increased[1]. However, no studies are seen using Sev. The purpose of this study was to compare the hemodynamic and catecholamine responses to rapid increase in inhaled concentration between Sev and Iso.

Materials and Methods: After the approval by our institutional review board and written informed consents, 30 patients scheduled for lower abdominal surgery were randomly divided into two groups; Sev group and Iso group (15 patients each). Anesthesia was induced with midazolam 0.1 mg/kg and thiopental 3 mg/kg and tracheal intubation was facilitated with vecuronium 0.15 mg/kg. Maintenance of anesthesia was done with epidural block using 1% mepivacaine, 67% nitrous oxide in oxygen, and Sev or Iso. When blood pressure and heart rate became stable, Sev or Iso concentration was kept in 0.5 MAC (minimum alveolar concentration, 1 MAC = 2.05% in Sev and 1.15% in Iso, end-tidal concentration measured by Ultima™, Finland) for 15 minutes. Suddenly Sev or Iso concentration (vaporizer setting) was changed to 1.5 MAC and it was kept for 10 minutes, then decreased to 0.5 MAC. Blood pressure (radial artery cannulation), heart rate (electrocardiogram), end-tidal concentration of Sev or Iso, and plasma concentrations of Ep and NEp (high performance liquid chromatography) were measured before, during and after the change of inhaled concentrations. For statistical analysis, chi-square test, unpaired t test, and two-way repeated-measures analysis of variance followed by Fisher's protected least significant difference were used and $p < 0.05$ was considered to be significant.

Results and Discussion: Decrease in blood pressure, increase in heart rate and increase in NEp concentration were significantly greater in Iso group than in Sev group. Ep concentration decreased in Sev group but not in Iso group, which had the significance between the two groups (figure). The sympathetic response to decreased blood pressure might be depressed in Sev anesthesia.



Closed:Iso, Open:Sev, SEM, *:P<0.05 vs Sev

Conclusions: Rapid increase in inhaled concentration of Iso induced sympathetic hyperactivity but that of Sev depressed sympathetic response.

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A.177 Which parameters unmask diastolic dysfunction in hypertensives during Valsalva manoeuvre as measured with Doppler sonography?

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Introduction: The first consequence of hypertension (HT) is a diastolic dysfunction of the left ventricle (LV) which can be assessed by analysis of the mitral flow pattern (E/A-ratio), the isovolumic relaxation time (IVRT) and the flow velocities in the pulmonary veins e.g. during systole (PV-VTI sys). None of these methods have been reported to be reliable in the absence of morphological changes of the left ventricle.

Patients and Methods: The changes of mitral flow pattern during Valsalva maneuver (VE/VA-ratio) in 5 groups of patients (n = 69) where measured. Patients were classified according to 24 h blood pressure (BP) and dopplersonographic measurements: 1. Normal: Patients with normal left ventricular mass (LVM) and normal BP. 2. Untreated hypertensives with normal LVM and relative wall index (RWI). 3. Hypertensives with normal LVM and high RWI (this reflects remodeling of the LV). 4. Hypertensives with concentric hypertrophy of the LV (abnormal LVM, RWI > 0.45). 5. Hypertensives with excentric left ventricular hypertrophy (abnormal LVM, RWI < 0.45). In all patients E/A-ratio, VE/VA-ratio, the IVRT and PV-VTI sys were assessed. A multiple regression model was generated in order to stratify the patients in the correct groups (1–5) using a stepwise backward elimination procedure.

Results: The E/A-ratio in hypertensives with normal LVM was normal at rest. However with the Valsalva maneuver we were able to show a significant difference between normotensives and untreated hypertensives. The measurement of VE/VA-ratio is sufficient to identify patients with a diastolic dysfunction of the left ventricle ($p < 0.05$), but does not provide sufficient information to stratify them to one of the groups 2–5.

Conclusion: Measurement of VE/VA-ratio using dopplersonography is a clinical useful tool to make a rapid diagnosis of diastolic dysfunction using a single parameter.

A.178 Effect of the insufflating gas on the release of vasopressin during laparoscopy in pigs

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Background & Goal of Study: During CO_2 pneumoperitoneum, haemodynamic changes result from both mechanical and humoral factors. The profile of the increase in vasopressin (VP) parallels the time course of systemic vascular resistances (SVR), suggesting a possible cause and effect relationship (1, 2). However, the trigger for VP release is unknown. We assessed the role of the insufflating gas and, in that way, investigated the relationship between haemodynamic changes and plasma concentration of VP during CO_2 and argon pneumoperitoneum in pigs.

Materials & Methods: 12 pigs (25–30 kg) were anaesthetized with enflurane 1.5%. Argon (n = 6) or CO_2 (n = 6). Pneumoperitoneum was created and maintained constant at 15 mmHg. Ventilation was controlled with a tidal volume of 15 ml/kg at a rate adjusted to obtain $PetCO_2$ of 28–34 mmHg and maintained constant for the remainder of the experiment. Haemodynamic variables were studied by Swan-Ganz and femoral arterial catheterisations. Arterial blood samples were collected before insufflation (Bas), 5 min (In5), 20 min (In20) and 40 min (In40) after the beginning of insufflation, 5 min (Ex5) and 30 min (Ex30) after exsufflation. Plasma lysine VP were measured by radioimmunoassay. Data were analyzed by ANOVA, Student's t test and Spearman's correlation.

Results & Discussion: VP and SVR increased markedly after insufflation of CO_2 pneumoperitoneum (table). There was a significant relationship between these variations ($r = 0.79$, $p < 0.005$). $PetCO_2$ continuously increased throughout the pneumoperitoneum but these variations were not related to changes in VP. VP, SVR and $PetCO_2$ remained stable during argon pneumoperitoneum. Changes in cardiac output and peak airway, right atrial and pulmonary capillary wedge pressures were not different in either group.

		Bas	In5	In20	In40	Ex5	Ex30
CO_2	SVR	2261	2958*	2642	2422	2151	1966
	VP	82	137*	105	93	77	72
Argon	SVR	2100	2252$	2138	2463	2280	2219
	VP	74	81$	68	56	89	60

*$p < 0.05$ versus baseline, \$$p < 0.05$ CO_2 versus argon

Conclusion: In pigs as in humans, the timing of VP release are consistant with a causative action to increase SVR during CO_2 pneumoperitoneum. It seems unlikely that the increase in VP is caused by changes in intrathoracic or intracardiac pressures. We suggest that absorbed CO_2 could be the major stimulus for the VP release during laparoscopy.

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A.179 Comparison of gastric-to-arterial ($(P(r\text{-}a)_{CO_2})$) and gastric-to-end tidal ($(P(r\text{-}et)_{CO_2})$) P_{CO_2} gap after cardiac surgery

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Background: Automatized P(r-et)CO_2 as measured with the Tonocap™ is now proposed as a non-invasive marker of gastrointestinal perfusion Increased P(r-et)CO_2 could reflect gastrointestinal hypoperfusion. However, it may be related to either increased P(r-a)CO_2 or increased arterial-to-end tidal PCO_2 gap [P(a-et)CO_2] This study aimed to evaluate in post-cardiac surgery patients, with (Gr1) or without (Gr2) circulatory failure, the significance of increased P(r-et)CO_2.

Methods: 14 patients undergoing elective cardiac surgery were monitored with arterial line and pulmonary artery catheter. Tonocap™ measured end-tidal CO_2 and regional PCO_2 *via* a nasogastric tonometer (Trip™ catheter). Mean arterial pressure (MAP, mmHg), O_2 supply (DO_2, ml/kg.mn), blood lactate (L, mmol/l) and arterial blood were measured every 2 hours during a 12 hour post-operative period The P(r-a)CO_2, P(r-et)CO_2 and P(a-et)CO_2 (mmHg) were calculated. Data (M ± SE) were analyzed using Wilcoxon and Mann-Whitney tests.

Results: In Gr1, as DO_2 failed to increase postoperatively, L, P(r-a)CO_2 and P(r-et)CO_2 increased. P(a-et)CO_2 tended to decrease In Gr2, DO_2 increased, and L, P(r-a)CO_2 and P(r-et)CO_2 tended to remain stable P(a-et)CO_2 tended to decrease as seen in Gr1 (Table).

	H0	H4	H8	H12
MAP				
Gr1	71.3 ± 6.4	72.4 ± 6.7	78.4 ± 3.8	85.1 ± 6.1
Gr2	68.4 ± 3.9	79.1 ± 7.1	75.1 ± 7.3	82.1 ± 5.9
DO_2				
Gr1	9.0 ± 1.6	8.7 ± 0.9	9.3 ± 1.1	9.0 ± 1.1
Gr2	7.8 ± 0.4	$10.7 \pm 0.3^{*}$	10.0 ± 1.0	$11.6 \pm 0.8^{*}$
L				
Gr1	3.7 ± 1.2	3.5 ± 1.3	3.5 ± 1.4	3.3 ± 0.8
Gr2	2.3 ± 0.5	2.3 ± 0.5	2.0 ± 0.3	2.5 ± 0.3
P(r-a)CO_2				
Gr1	$10.1 \pm 1.9^{\#}$	17.3 ± 4.3	$21.4 \pm 3.9^{\#*}$	18.0 ± 7.4
Gr2	3.3 ± 1.0	$8.6 \pm 1.8^{*}$	$12.2 \pm 3.0^{*}$	$10.7 \pm 0.7^{*}$
P(r-et)CO_2				
Gr1	$18.4 \pm 3.0^{\#}$	$26.3 \pm 4.7^{*}$	$28.4 \pm 4.9^{\#*}$	22.1 ± 8.0
Gr2	12.3 ± 1.6	14.1 ± 3.3	$15.6 \pm 1.6^{*}$	12.1 ± 1.2
P(a-et)CO_2				
Gr1	11.8 ± 3.4	9.0 ± 2.0	$7.0 \pm 1.3^{\#}$	$4.2 \pm 1.4^{*}$
Gr2	9.0 ± 1.7	6.3 ± 1.8	$3.3 \pm 0.4^{*}$	$2.3 \pm 0.8^{*}$

$^{*}p < 0.05$ vs H0-Hx; $^{\#}p < 0.05$ GR1 vs Gr2

Conclusion: After cardiac surgery, circulatory inadequacy is associated with a widening in P(r-et)CO_2 suggesting decreased gastrointestinal perfusion This is related to an exclusive increase in P(r-a)CO_2. In this study, the P(r-et)CO_2 gap appears to provide a useful non-invasive index of gastrointestinal perfusion.

A.180 Gastric mucosal hypoperfusion during cardiopulmonary bypass is associated with increased postoperative cardiovascular morbidity

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Background and Goal of Study: During cardiopulmonary bypass (CPB) gastric mucosal perfusion, assessed by Laser Doppler flowmetry, decreases (1). The hypothesis was that patient with high decrease in gastric mucosal perfusion, and probably inadequacy between oxygen delivery and consumption, may have a postoperative period worsen than patient with a low decrease. In our study we have recorded vasoactive medication consumption to treat hypotension or low cardiac index in post operative period.

Methods: The study was conducted in 43 patients during elective cardiac surgery It was a prospective descriptive study. After general anaesthesia, a pulmonary artery catheter (Baxter®) and the gastric Laser Doppler probe (probe 424, Perimed®) was inserted. The Laser Doppler signal is proportional to the number of red blood cells moving in the measured volume and the mean velocity of the cells. The group high decrease was defined as gastric perfusion less than 50% (100% was pre CPB value) and the group low decrease was defined as gastric perfusion more than 50% during CPB. CPB was managed with a non pulsatile flow at 2.4 L/min/m² with a MAP between 60 and 90 mmHg in moderate hypothermia (30–32°C) Data were recorded in postoperative period 1) cardiac index at admission in ICU, 2) need for vasoactive medication to treat hypotension or low cardiac output (dopamine more than 3 μg/kg/min, dobutamine more than 3 μg/kg/min, norepinephrine, epinephrine), 3) time to intensive care unit (ICU) discharge.

Results: Results are expressed in the table

	High decrease	Low decrease	*P*
Gastric Perfusion at 30 min CPB (%)	40 ± 13	$72 \pm 14^{*}$	<0.001
Cardiac index (L/min/m²)	2.1 ± 0.2	$2.7 \pm 0.5^{*}$	0.02
Vasoactive med (n)	13/20	5/23*	<0.001
ICU discharge (days)	3.6 ± 1.6	3.2 ± 1.5	0.12

Conclusion: Results of our study suggested that patient who have a high gastric hypoperfusion during CPB have a greater cardiovascular morbidity during the postoperative period These major hypoperfusion might be associated with gastric mucosal injury

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A.181 Increased gastric-to-arterial P_{CO_2} gap ($(P(r\text{-}a)_{CO_2})$) predicts occurrence of circulatory failure after cardiac surgery

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Background: P(r-a)CO_2 has been proposed as a marker of gastrointestinal perfusion adequacy The aim of the study was to compare, retrospectively, P(r-a)CO_2 with conventional monitoring and venous-to-arterial PCO_2 gap [P(v-a)CO_2] in patients with (Gr1) or without (Gr2) circulatory failure after cardiac surgery.

Materials and Methods: 14 patients undergoing elective cardiac surgery, with inserted arterial line and pulmonary artery catheter, were included in the study. Circulatory failure was defined as requirement for vasoactive support. Mean arterial pressure (MAP, mmHg), cardiac output (CO, l/min m²), blood lactate (L, mmol/l) and arterial blood gas were measured every two hours during a 12-hour post-operative period. PrCO_2 was monitored as well with the Tonocap™ *via* a nasogastric tonometer (Trip™ catheter) P(r-a)CO_2 and P(v-a)CO_2 (mmHg) were calculated. Data (mean ± SE) were analyzed using Wilcoxon and Mann-Withney tests.

Results: In response to increased O_2 requirements, CO increased significantly in Gr2 but did not change in Gr1. L tended to be higher in Gr1. P(r-a)CO_2 was larger in Gr1 at HO and was the sole parameter to be different between Gr1 and Gr2 at H0. Furthermore, it increased to a larger extent in Gr1 from H0 to H12. P(v-a)CO_2 did not vary significantly (Table).

	H0	H4	H8	H12
MAP				
Gr1	71.3 ± 6.4	72.4 ± 6.7	78.4 ± 3.8	85.1 ± 6.1
Gr2	68.4 ± 3.9	79.1 ± 7.1	75.1 ± 7.3	82.1 ± 5.9
CO				
Gr1	2.7 ± 0.4	2.6 ± 0.3	2.7 ± 0.3	$2.6 \pm 0.3^{\#}$
Gr2	2.5 ± 0.3	3.1 ± 0.3	3.0 ± 0.2	$3.4 \pm 0.2^{*}$
L				
Gr1	3.7 ± 1.2	3.5 ± 1.3	3.5 ± 1.4	3.3 ± 0.8
Gr2	2.3 ± 0.5	2.3 ± 0.5	2.0 ± 0.3	2.5 ± 0.3
P(r-a)CO_2				
Gr1	$10.1 \pm 1.9^{\#}$	17.3 ± 4.3	$21.4 \pm 3.9^{\#*}$	18.0 ± 7.4
Gr2	3.3 ± 1.0	$8.6 \pm 1.8^{*}$	$12.2 \pm 3.0^{*}$	$10.7 \pm 0.7^{*}$
P(v-a)CO_2				
Gr1	7.7 ± 1.2	9.6 ± 1.8	9.3 ± 1.4	4.9 ± 2.2
Gr2	6.9 ± 0.7	8.1 ± 0.5	6.7 ± 1.1	5.4 ± 0.7

$^{*}p < 0.05$ vs H0-Hx, $^{\#}p < 0.05$ Gr1 vs Gr2

Conclusion: Increased P(r-a)CO_2, after cardiac surgery, is rapidly associated with requirements for vasoactive therapy. Since P(v-a)CO_2 did not change, increased P(r-a)CO_2 suggests a selective hypercarbia in gastrointestinal tract consecutive to diverted blood flow to vital organs This marker may be an early indicator of gastrointestinal hypoperfusion and could help to optimize treatment in circulatory failure

A.182 Systemic and regional tissue perfusion in response to increasing metabolic demands after cardiac surgery

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Objective: To assess the adequacy of systemic, regional and local splanchnic perfusion after cardiac surgery

Materials and Methods: 17 patients after coronary bypass (CABG) surgery were studied Systemic (PA catheter) and regional (dye dilution) hemodynamics and O_2-transport and gastric mucosal pCO_2 (tonometry) were measured every three hours from arrival to the ICU until extubation

Results and Discussion: Systemic VO_2 increased from 126 ± 20 to 136 ± 16 ml/min m² ($p = 0.028$) Lactate/pyruvate ratios (L/P) were initially high in all vascular beds. Splanchnic O_2-extraction was high and increased despite stable systemic and decreasing femoral O_2-extraction Splanchnic L/P decreased but the hepatic vein-arterial pCO_2 gap increased.

	Baseline	3 h	6 h	p
Flows (l/min m²)				
– systemic	2 9 ± 0 7	3 1 ± 0 6	3 2 ± 0 6	
– splanchnic	0 7 ± 0 2	0 7 ± 0 2	0 6 ± 0 1	
– femoral	0 2 ± 0 1	0 2 ± 0 1	0 2 ± 0 1	
O2 extraction (%)				
– systemic	0 3 ± 0 1	0 3 ± 0 1	0 3 ± 0 1	
- splanchnic	0 4 ± 0 2	0.5 ± 0 1	0 5 ± 0 1	0 018
– femoral	0 4 ± 0 1	0 3 ± 0 1	0 3 ± 0 1	0 020
pCO2 gaps (kPa)				
– hepatic v – a	0 5 ± 0 2	0 5 ± 0 1	0 6 ± 0.2	0 019
– femoral v – a	1 1 ± 0 3	1 0 ± 0 3	1 0 ± 0 3	
– mucosal – a	0 5 ± 1 1	0 6 ± 0 7	0 6 ± 0 6	
L/P				
– arterial	14 ± 2 3	14 ± 2 8	12 ± 1 0	<0 001
– hepatic	18 ± 15	11 ± 3 3	11 ± 4 0	0 047
– femoral	17 ± 2 4	16 ± 2 7	15 ± 2 5	

Statistics MANOVA for repeated measurements

Conclusions: Metabolic demands increase after CABG. Regional L/P and pCO2 gaps indicated marginal tissue perfusion. Splanchnic tissue perfusion remains at risk early after CABG despite stable systemic hemodynamics

A.183 Can pharmacological intervention re-establish splanchnic blood flow during carbon dioxide-pneumoperitoneum? An experimental model

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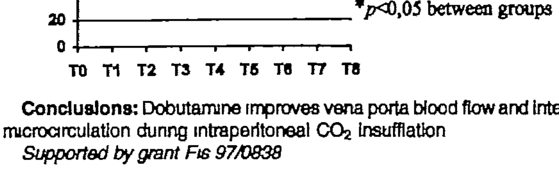
Background: Elevated intraabdominal pressure (IAP) due to gas insufflation may result in splachnic blood flow impairment.

Goal of Study: To investigate the role of beta-adrenergic drugs on splanchnic blood flow and intestinal mucosa microcirculation during CO_2-pneumoperitoneum.

Materials and Methods: 18 pigs, weighting 25–30 kg, were anesthetized and mechanically ventilated. Peritoneal cavity was insufflated with CO_2 at 15 mmHg during 1 hr. Then, the animals were randomized in two groups of 9 pigs each one. Dopamine (AG) and dobutamine (BG) at 5 µg/kg/min, respectively, were infused during 30 min. The follow variables were analyzed hemodynamic parameters, hepatic artery blood flow (HBF), superior mesenteric artery blood flow (SMABF) and vena porta blood flow (VPBF) with perivascular flowmeter, and intestinal microcirculation with laser-Doppler flowmetry These variables were recorded at baseline (T0), at 15, 30, 45 and 60 min (T1, T2, T3, T4), at 15 and 30 min after started vasoactive drug infusion (T5, T6) and at 15 and 30 min after stopped infusion (T7, T8). Statistical analysis with paired t test were performed

Results: HBF, SMABF, VPBF and intestinal microcirculation decreased with gas insufflation in all times respect to baseline ($p < 0.05$). Any vasoactive drug used modified HBF and SMABF. Only Dobutamine increased VPBF ($p < 0.05$). The changes of intestinal microcirculation are shown in figure.



Conclusions: Dobutamine improves vena porta blood flow and intestinal microcirculation during intraperitoneal CO_2 insufflation

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A.184 Impact of ventilation with positive end-expiratory pressure on splanchnic oxygenation

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Background and Goal of Study: To evaluate if normalization of cardiac output (CO) reverses the attenuation of local intracapillary haemoglobin saturation (HbO_2) of gastric mucosa by PEEP (Positive End-Expiratory Pressure) during IPPV (Intermittent Positive Pressure Ventilation).

Materials and Methods: Four healthy, anaesthetized dogs were repeatedly studied (7 experiments) The animals were chronically instrumentated with carotid loops and an ultrasonic flowprobe implanted around the pulmonary artery to allow the continuous measurement of systemic mean arterial pressure (MAP) and CO We continuously measured HbO_2 of gastric mucosa (EMPHO II, Erlanger Microlightguide Spectrophotometer)[1] and total body oxygen consumption (VO_2, Datex Deltatrac™, Datex Instrumentation Corp., Helsinki, Finland) Arterio-venous oxygen content difference ($C_{(a-v)}O_2$) could be derived from CO and $\dot{V}O_2$ After obtaining baseline values during IPPV and ZEEP (Zero End-Expiratory Pressure) PEEP (15 cmH_2O) was added To compensate the reduction of CO due to PEEP, HES (hydroxyethyl starch 6%) was infused until CO reached baseline values during ZEEP

Results and Discussion: Despite of unimpaired systemic oxygen saturation, PEEP reduced HbO_2 of gastric mucosa from 55.1 ± 4 2% to 42.1 ± 4.7% (mean ± SEM). CO dropped from 67 7 ± 4 9 ml min^{-1} kg^{-1} to 33.9 ± 4 6 ml min^{-1} kg^{-1} and MAP from 66 4 ± 1 1 mmHg to 51.3 ± 2 4 mmHg. $C_{(a-v)}O_2$ increased simultaneously from 6.4 ± 0 2 ml 100 ml^{-1} to 10.8 ± 2.0 ml 100 ml^{-1}. Whereas infusion of HES during PEEP ventilation not only normalized CO to baseline values, but MAP and $C_{(a-v)}O_2$ as well, HbO_2 reached only 48.1 ± 3.3%, a statistically significant improvement compared to HbO_2 during ventilation with PEEP before HES infusion ($p < 0.05$, Wilcoxon signed rank test), but still below baseline values ($p < 0\ 05$).

Conclusions: Our findings demonstrate that the side effects of PEEP on systemic circulation can be fully compensated by restoring preload But normalizing systemic flow and pressure did not completely normalize HbO_2 of gastric mucosa. This further emphasizes that global measurements of variables of systemic circulation and oxygenation do not necessarily reflect regional abnormalities of tissue oxygenation. Therefore, in view of the utmost importance of dysoxia especially in the splanchnic region in the pathogenesis of multiple organ dysfunction syndrome, monitoring of HbO_2 of intestinal mucosa during ventilation with PEEP may be particularly useful in the care of the critically ill patient

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A.185 Comparison of endothelial function in the internal mammary artery and the radial artery

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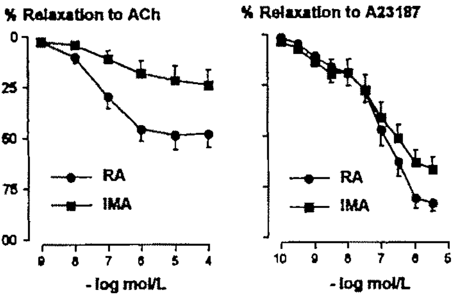
Background and Goal of Study: We have previously found that internal mammary arteries (IMA) exhibit substantial variability of endothelium-dependent vascular relaxation. Recently, the use of radial artery (RA) grafts for CABG has been reintroduced The long-term patency of these grafts may depend on the ability of these vessels to produce nitric oxide (NO), which has anti-atherosclerotic properties We therefore sought to determine if RA might exhibit a more preserved endothelial function as compared to the IMA.

Material and Methods: In vitro isometric tension studies were performed on RA (n = 5) and IMA (n = 67) segments from patients undergoing CABG. Vessels were preconstricted with the thromboxane analogue U466 19 (10 nM) and exposed to increasing concentrations of either acetylcholine (ACh), calcium ionophore A23187, or nitroglycerin.

Results & Discussion: Both RA and IMA relaxed 100% of the preconstricted tension to nitroglycerin. As shown in figure 1, endothelium-dependent vascular relaxations to ACh and A23187 were substantially greater in the RA (50 ± 7 and 88 ± 5% respectively) as compared to the IMA (23 ± 7 and 69 ± 5%, respectively, $p < 0.05$ vs RA for both). The RA was also more reactive to vasoconstrictors than the IMA, including (all maximum responses in grams) KCl (10 ± 1 vs 2 ± 0), and thromboxane analogue (14 ± 1 vs 4 ± 1).



Conclusion: RA is much more vasoactive than the IMA. The enhanced endothelium-dependent vascular relaxation may have implications for the long term patency of RA grafts as endothelium-derived nitric oxide inhibits intimal proliferation and atherosclerosis. The increase in vasoconstrictor responses of the RA may predispose these vessels to spasm and suggests that the use of vasodilator therapy after RA graft placement may be beneficial

A.186 Pressure-flow relationship of arterial and venous bypass grafts: influence of volume changes and pharmacological vasodilatation

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Purpose: To evaluate the influence of perfusion pressure and volume changes on intraoperative coronary blood flow and coronary flow reserve of arterial and venous bypass grafts.

Methods: Coronary blood flow was measured in 20 consecutive patients undergoing myocardial revascularisation for coronary artery disease. Flow measurements (transit time; CardioMed, Medi-Stim, Norway) were performed after discontinuation of cardiopulmonary bypass (CPB) in the IMA graft to LAD and in saphenous vein grafts at different aortic pressures induced by CPB volume changes [1]. Coronary flow reserve (CFR) was measured during maximal vasodilation at increasing doses of adenosine (2, 11, 23 μg/kg/min) Aortic pressure was kept constant by controlled CPB volume infusion during adenosine administration

Results: (1) Resting flow in the IMA graft was 33 ± 13 ml/min and coronary resistance 2.8 ± 1.9 Ω Flow in the vein graft was 68 ± 31 ml/min and resistance 1.4 ± 0.7 Ω (MAP = 75 ± 7 mmHg).

(2) A linear pressure-flow relationship was found for arterial ($r = 0.59$, $p < 0.02$ at maximal adenosine dosis) and venous ($r = 0.56$, $p < 0.06$) bypass grafts

(3) Coronary flow reserve was 1.7 for the IMA and 1.6 for the vein grafts. In the 20 patients a normal CFR (>2 0) was observed in 5 ima and in 6 venous coronary grafts

(4) Adenosine showed a dose-dependent effect on CFR: 2 μ/kg/min IMA 1.1, SVG 1 0; 11 μ/kg/min: IMA 1 3, SVG 1.4; 23 μg/kg/min. IMA 1.4, SVG 1 5; 23 μ/kg/min with infusion of volume· IMA 1 7, SVG 1 6.

Conclusions: Intraoperative flow measurement can be accurately obtained by the transit time technique. A normal coronary flow reserve was observed only in 30% of all patients due to relatively high resting flow (graft and native vessel). A linear pressure-flow relationship was found for arterial and venous grafts at maximal pharmacologic vasodilation

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A.187 Haemodynamic effects, myocardial ischaemia, and timing of extubation with TIVA propofol-sufentanil *vs* midazolam-sufentanil-isoflurane anaesthesia for CABG surgery

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Background: Fundamental principles of anesthesia for coronary artery bypass graft (CABG) surgery include maintaining hemodynamic stability and minimizing myocardial ischemia. To provide anesthesia, an opioid is usually delivered in combination with a hypnotic drug or potent inhalational anesthetic The effects of TIVA (total intravenous anesthesia) propofol-sufentanil anesthesia versus midazolam-sufentanil-isoflurane anesthesia were evaluated and compared.

Methods: We randomized 44 patients, ASA grade 2 or 3, undergoing CABG surgery to receive either propofol-sufentanil anesthesia (propofol 5 mg/kg/h prior to sternotomy, 3 mg/kg/h thereafter [n = 24] and sufentanil 0 2 μg/kg for induction, 0 2–0 6 μg/kg/h for maintenance, total doses 5 μg/kg), or midazolam (30 μg/kg/h from induction to skin closure), sufentanil (max total doses 7 μg/kg) and isoflurane 0.5–2 vol% Hemodynamic (mBP, HR, CPV, PCWP, CI, SVRI, PVRI) and ECG were determined in seven time periods. II, aVL and V_5 ST-segment analysis was used for the detection of myocardial ischemia.

Results: The measured cardiovascular parameters were satisfactory and usually similar for both groups. The percentage of patients with intraoperative ST-segment deviation (15 ± 3% vs. 14 ± 4%) did not differ significantly between the two groups. The incidence of intraoperative hypotension (62% vs. 51%, $p = 0\ 01$), the use of inotropic/vasopressor medications (70% vs. 60%) were significantly greater in the propofol-sufentanil group The incidence of hypertension (43% vs 52%, $p < 0.01$) and the use of antihypertensive medications were significantly less in the propofol-sufentanil group The midazolam-sufentanil-isoflurane group received greater total doses of sufentanil (7 μg/kg vs 5 μg/kg, N.S.). Patients receiving propofol were extubated earlier, median 10 1 h vs. 12.1 h; $p = 0.005$.

Conclusions: The study suggest that most patients undergoing CABG surgery can be safely anesthetized with TIVA propofol-sufentanil without increased intraoperative myocardial ischemia, increased hypotension or hypertension, compared to an midazolam-sufentanil-isoflurane technique requiring greater dosing of sufentanil.

A.188 Effects of remifentanil and fentanyl on perioperative oxygen consumption in patients undergoing myocardial revascularization

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Background and Goal of Study: Remifentanil has been shown to obtund major stress events during cardiac anaesthesia when used in combination with propofol. The purpose of this study was to measure the oxygen consumption (VO_2) of patients receiving remifentanil during CABG surgery and to compare it with that of patients receiving fentanyl

Materials and Methods: Using a randomised, double blind, comparative design, 12 patients with ejection fractions >0 35 undergoing elective CABG surgery were randomised to receive either remifentanil (group R: n = 6) or fentanyl (group F· n = 6) analgesia Following induction with propofol (0 5 mg/kg) and relaxation with pancuronium (0.15 mg/kg), anaesthesia was maintained with a propofol infusion (3 mg/kg/hr). Group R received an infusion of remifentanil (rate 1 μg/kg/min) with simultaneous boluses of placebo equivalent in volume to the fentanyl given in group F Group F received an induction bolus of fentanyl (15 μg/kg) followed by further maintenance boluses (2 μg/kg) with a simultaneous infusion of placebo equivalent in volume to the remifentanil given in group R. The protocol required that the rate of infusion of remifentanil and the number of boluses of fentanyl were adjusted to maintain control of cardiovascular indices within tight limits both on and off cardiopulmonary bypass Hypothermic (T = 28°C), non-pulsatile perfusion with crystalloid cardioplegia were used VO_2 was measured using the Datex Deltatrac CI, MPAP and SvO_2 were measured using an Oximetrics multilumen pulmonary artery flotation catheter. VO_2, CI, SvO_2, MPAP, IABP, MAP and HR were recorded after induction of anaesthesia (T1), after sternal incision (T2), immediately prior to giving protamine post bypass (T3) and immediately prior to transfer to the ICU (T4).

Results and Discussion: The two groups were matched for age, weight, length of surgery and bypass variables. Mean VO_2 was unchanged at T1 and T2 and equal in both groups Between T2 and T3 mean VO_2 rose from 90.2 to 122 2 ml/min/m^2 ($p < 0.01$) in group F but remained close to baseline levels in group R (T2 88 2, T3 92 2 ml/min/m^2). Mean VO_2 was significantly higher in group F than in group R at T3 (F 122 2 ml/min/m^2 R 90.2 ml/min/m^2 [$p < 0.01$]) Between T2 and T3 mean CI rose significantly in both groups (R· 2.0 to 2 7l/min/m^2 F 2.0 to 2 9l/min [$p < 0.01$]). Mean SvO_2 fell in group F (from 80.3 to 74.3%; $p = 0.04$) but remained unchanged in group R. There were no significant differences in mean HR, MAP or MPAP between the two groups at T3 Despite a similar rise in cardiac index in both groups, oxygen consumption remained close to baseline levels in the remifentanil group

Conclusion: The low oxygen consumption seen with remifentanil may have important implications for patients who have a reduced oxygen supply associated with either impaired gas exchange or poor myocardial function.

A.189 Myocardial protection during coronary artery bypass graft surgery with thoracic epidural analgesia

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Background and Goal of Study: TEA encourages a favourable pattern of coronary artery blood flow via selective vasodilation of stenotic atherosclerotic segments [1], increased subendocardial perfusion [2] and, as shown in animal models, a subsequent reduction in infarct size [2, 3]. Attenuation of the stress response, with reduced post cardiopulmonary bypass (CPB) catecholamine levels (CA's), may reduce coronary vasoconstriction distal to stenoses – shown to have an upregulated α-receptor profile. Our aim was to determine whether the proposed beneficial effects of TEA could reduce perioperative ischaemic injury with improved cardiac outcome.

Methods: Following ethical approval, 20 CABG patients (NYHA II or III, LVEF > 50%) were randomised to general anaesthetic (GA) (n = 10) using fentanyl (10–15 mcg/kg), propofol and isoflurane or a TEA (n = 10) (C7-T1 – 0.1 ml/kg 0.5% bolus + 0.1% infusion bupivicaine + 2 mcg/ml fentanyl for 72 hours following surgery) combined with intra operative intravenous propofol infusion. Two channel holter monitoring for ST segment elevation (>2 mm) and depression (<1 mm), pulmonary artery catheter derived haemodynamics, troponin-I (cTn-I), creatine kinase (CK and CK-MB) and CA's were measured at defined time points over 72 hours. Pre and post operative ECGs were recorded up to 6w following surgery

Results: Haemodynamic parameters, CK-MB, preoperative ST segment changes and postoperative ST segment depression revealed no differences between groups Postoperatively there was a significant **reduction** in both the degree ($p < 0.04$) and duration ($p < 0.005$) of ST segment elevation, CA's (noradrenaline; $p < 0\ 05$ @ 1, 12, 24 h post CPB), cTn-I ($p < 0.05$ @ 6 h post CPB; 3 5 ± 0 6 vs. 12.4 ± 4.2 ng/ml;), total CK ($p < 0\ 05$ @ 1, 3, 6, and 72 h post CPB) in the TEA group One new perioperative myocardial infarction was suffered in the GA group.

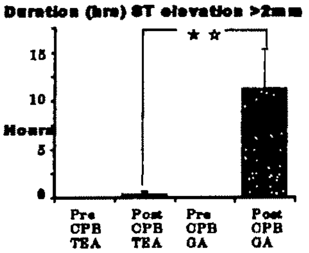

Figure 1 Duration (hours) of ST segment elevation (<2 mm) following CPB; mean ± sem for 72 h post CPB, ** = $p < 0\ 005$ [Mann-Whitney-U test]

Conclusions: The TEA group demonstrated a significant reduction in post CPB coronary vasoconstriction, as measured by surrogate markers of ischemia (cTn-I, ST segment elevation), which may relate to the direct vasodilatory effects of TEA, or a reduction in CA's The contributions to coronary vasoconstriction by endothelial dysfunction (associated with atherosclerosis and ischemia-reperfusion injury) were not explored Whether TEA may potentially confer a better postoperative cardiac outcome following CABG demands further study in a larger population

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A.190 Effects of hypothermic rewarming phase during cardiopulmonary bypass on cerebral perfusion and cerebral oxygenation

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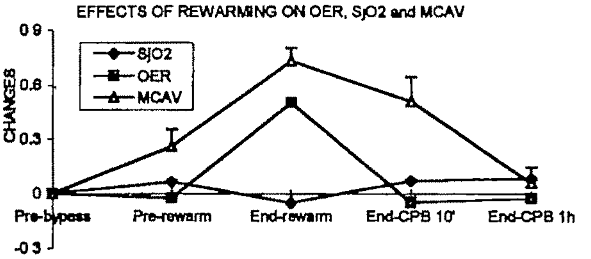
Background & Goal of Study: It is known that hypothermia itself minimises cerebral damage However, rewarming may be harmful. We therefore investigated the effect of hypothermic versus normothermic bypass on cerebral perfusion and oxygenation.

Material & Methods: 16 patients undergoing elective coronary bypass were randomised into hypothermic (28°C n = 9) and normothermic (37°C n = 7) groups. Transcranial Doppler measurements of Middle Cerebral Artery Velocities (MCAV) were used to estimate cerebral perfusion. Blood gas measurements of simultaneous arterial and jugular bulb samples were used to evaluate cerebral oxygenation Samples were taken before bypass, before rewarming and at end-rewarm for the hypothermic group, and before bypass and after 30 and 60 minutes of bypass for the normothermic group. MCAV and samples were taken 10 minutes and then 1 hour after bypass Oxygen Exaction Ratio (OER) was calculated using a standard equation. All values were normalised to 100% of pre-bypass values as a baseline to indicate the differences between two bypass techniques The data were analysed using the Mann-Whitney U test.

Results & Discussion: There was a significant increase in MCAV and OER, but a significant fall in jugular bulb oxygen saturation (SjO_2) at end-rewarm (Fig. 1). The increase in cerebral perfusion and oxygen extraction may protect the brain against ischaemia during rewarming.



Conclusions: MCAV & OER were increased and SjO_2 fell during hypothermic rewarming phase.

A.191 Effects of hypothermic rewarming phase during cardiopulmonary bypass on NSE and S-100 release and cerebral lactate production

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Background & Goal of Study: It is known that hypothermia itself minimises cerebral damage. However, rewarming may be harmful Neurone-Specific Enolase (NSE) and S-100 are showing promise as specific markers of neuronal and glial cell damage following cardiac surgery[1] Cerebral hypoxia leads to the release of lactate from the brain[2]. The aim of this study was to explore the effect of hypothermic versus normothermic bypass on cerebral release of NSE, S-100 and lactate

Material & Methods: 16 patients undergoing elective coronary bypass were randomised into hypothermic (28°C n = 9) and normothermic (37°C n = 7) groups. Simultaneous arterial and jugular bulb blood samples were taken, before bypass, before rewarming and at end-rewarm for the hypothermic group, and before bypass, after 30 and 60 minutes of bypass for the normothermic group Samples were also taken 10 minutes and then 1 hour after bypass. Serum NSE & S-100 levels were measured using radioimmunoassay, and serum lactate using an enzymatic technique. Cerebral lactate production was expressed as the difference between jugular bulb and arterial levels. All values (apart from temperatures) were normalised to 100% of pre-bypass values as a baseline to indicate the differences between two bypass techniques. The data were analysed using the Mann-Whitney U test

Results & Discussion: There was no difference between the two groups with regard to age, gender, duration of bypass and clamping time There were no significant differences in NSE & S-100 levels and cerebral lactate production between the two groups.

Conclusions: Effect of rewarming on cerebral release of NSE, S-100 and lactate did not differ from that of normothermic bypass.

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A.192 Effect of dexamethasone on extravascular fluid content after cardiopulmonary bypass

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Introduction: Cardiopulmonary bypass (CPB) causes a systemic inflammatory response with increased capillary permeability and accumulation of interstitial fluid. Specially, whole body oedema resulting from redistribution of body water between intra- and extravascular space or external fluid overload can lead to impaired organ function and postoperative morbidity[1]. This study was undertaken to determine the amount of oedema and to investigate if dexamethasone prevents fluid extravasation by suppression of inflammatory response[1].

Method: After ethical committee approval and written informed consent, twenty patients undergoing elective coronary bypass surgery were included in a randomised double-blind trial. Induction of anaesthesia was performed with 2 $\mu g \cdot kg^{-1}$ sufentanil and 0 1 $mg \cdot kg^{-1}$ pancuronium. Subsequently ten patients received placebo (plc) and the other ten 1 mg kg^{-1} body weight dexamethasone (dxm) Total blood volume (*TBV*) was estimated from hepatic elimination rate of indocyanine green[2] The amount of changes in extravascular body water ($\Delta EVBW$) was calculated from the difference between changes in total plasma volume and the corresponding net fluid balances. Measurements were carried out after induction of anaesthesia (A) and one (1 h), six (6 h), and twenty (20 h) hours after surgery. Statistical analysis was performed by 2-way ANOVA (repeated measures design).

Results: In the following table the changes of volume parameters are given as mean ± standard deviation

ΔTBV	A	1 h post OP		6 h post OP		20 h post OP	
[ml/kg] plc	0	−12 69	19 73*	−18 18	16 72**	−16 85	24 45**
dxm	0	−12 57	17 47*	−12 64	16 54*	−15 00	17 69**

* (**) $p < 0$ 05 (0 01) 1 h, 6 h, 20 h vs A

ΔEVBW							
[ml/kg] plc	0	58 80	13 55$	69 67	27 85$	55 57	25 46$
dxm	0	43 44	15 33$,#	48 94	18 26$,##	44 26	23 62$

$ $p < 0$ 001 1 h, 6 h, 20 h vs A, # (##) $p < 0$ 01 (0 001)· plo vs dxm

TBV decreased significantly after surgery in both groups Despite identical net fluid balances, in plc-group postoperative formation of tissue oedema exceeded that in dxm-group significantly

Discussion: This study demonstrates that whole body oedema formation can significantly be suppressed by pretreatment with corticosteroids Dexamethasone reduced accumulation of interstitial fluid obviously by inhibition of mediator triggered capillary leakage, which seems to be the main pathogenetic factor[1] of the inflammatory response to CPB

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A.193 Pulmonary endothelial cytoprotection by fructose-1,6-diphosphate in cardiac surgery

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Background and Goal of Study: Cardiopulmonary bypass (CPB) may produce an **ischemia-reperfusion (IR) injury** to the pulmonary [1], coronary, and other vascular endothelium resulting in endothelial activation and expression of proinflammatory factors e g leukocyte adhesion molecules, procoagulant and vasoconstrictive factors Pulmonary vasoconstriction [2], increased RV-afterload and impaired RV-performance may follow **Fructose-1,6-diphosphate** (FDP), an intermediary glycolytic pathway moiety has cytoprotective effects through enhanced anaerobic ATP production, oxygen burst inhibition, modulation of leukocyte-endothelial cell interaction and preservation of endothelial barrier integrity [3]. We investigated whether FDP reduced CPB-associated ischemic changes, providing cytoprotection to the pulmonary endothelium and thereby prevent postoperative pulmonary vasoconstriction, as measured by pulmonary vascular resistance (PVRI).

Materials and Methods: 30 consenting, elective, CABG patients (LVEF > 45%) were randomised to FDP (250 mg/kg ivi) or 5% Dextrose (placebo) treatment prior to CPB in this ethically approved, double blind clinical trial

Results and Discussion: Both groups were similar with respect to age, CPB and aortic cross-clamp duration

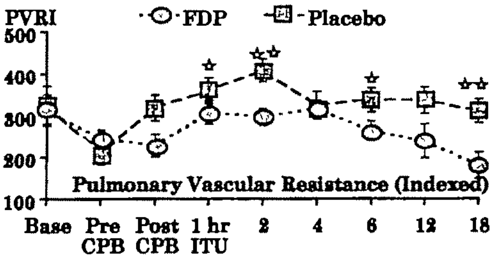

Figure PVRI, mean ± SEM, * = t [0 05, 29], ** = t [0 01, 29]

FDP attenuated mean PVRI (figure) increase for all patients and for subgroups with CPB < 90 or > 90 minutes, i e. 96 & 109 (FDP) vs. 112 & 141 (placebo) % of baseline values, respectively ($p = 0.017$, AUC; chi square analysis).

Conclusions: This data suggests that (i) the severity of postoperative pulmonary vasoconstriction relates to CPB duration and (ii) that FDP beneficially reduces PVRI and subsequent RV-afterload in the early postoperative period

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A.194 Propofol inhibits myocardial lipid peroxidation during coronary artery bypass grafting surgery

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Goal of the Study: To determine if propofol, when used for anaesthesia maintenance, acts as a free radical scavenger during coronary bypass grafting (CABG) surgery

Materials and Methods: Twenty-four patients assigned for CABG surgery having three major coronary artery occlusions and ejection fraction greater than 45% were selected for the study Patients in the control group (Fentanyl group, n = 14), after induction with fentanyl 10 mg/kg, midazolam 0.1 mg/kg, pancuronium 0.08 mg/kg, received fentanil infusion 10–30 mg/kg/hr, midazolam 0.1 mg/kg every 60 minutes, and pancuronium 0 04 mg/kg every 45 minutes for the maintenance of anaesthesia. Patients in the Propofol group (n = 10) after induction with the same drugs, received propofol infusion 3–6 mg/kg/hr, midazolam 0.1 mg/kg every 60 minutes, and pancuronium 0.04 mg/kg every 45 minutes for maintenance of anaesthesia during CABG surgery 0 2 g of atrial tissue biopsy is taken during cannulation for bypass, cross-clamp when the patient's rectal temperature was 29°C, after cross-clamp removal, and after decannulation Lipid peroxidation is assessed by the method of Mihara and Uchiyama in the atrial tissue samples.[1]

Results: The results of mean (± SD) lipid peroxidation levels during cannulation, cross-clamp, cross-clamp removal and decanulation in the fentanyl group were 45 6 ± 7.9, 63 6 ± 15 9, 74 5 ± 14.9, 72 8 ± 16 and in the propofol group were 34 4 ± 7 2, 38 9 ± 18 2, 43.9 ± 16 8, 43 8 ± 13 6 (nmols/gr wet tissue) respectively. In all sampling periods lipid peroxidation levels in the propofol group were lower than fentanyl group ($p < 0.05$) Although lipid peroxidation levels in the fentanyl group increased significantly ($p < 0$ 05) during CABG surgery, propofol group showed no increases ($p > 0$ 05).

Conclusion: Eventhough inhibition of lipid peroxidation by propofol is a known fact,[2,3] this was not shown in vivo during CABG surgery, in which reperfusion injury is a major problem We conclude that propofol is a potent inhibitor of lipid peroxidation during CABG surgery even in the lower maintenance doses.

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A.195 Is load dependence of rate of left ventricular relaxation coupled to contractile function in coronary surgery patients?

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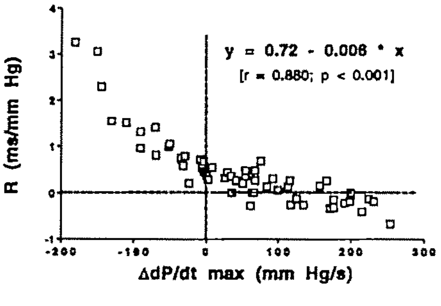
Background: Left ventricular (LV) relaxation rate is more dependent on systolic load in the failing heart than in the normal heart (1) It was suggested that this dependence might provide a clinical tool to evaluate individual cardiac function (2) The present study evaluated whether dependence of rate of LV relaxation on systolic pressures would allow estimation of individual LV contractile function in patients undergoing coronary surgery (CABG).

Methods: Patients (n = 80) with preoperative ejection fraction >40% were included LV pressures were measured with a tipmanometer inserted in the LV cavity. Paced heart rate was 90 beats/min. LV pressures were recorded during leg elevation, resulting in an increase of LV pressures The effects of leg elevation on myocardial function were evaluated by the changes in LV pressure and dP/dt_{max}. Effects of leg elevation on rate of LVP fall were evaluated by the changes in the time constant τ of isovolumic relaxation. Time constant τ was linearly fit to the corresponding end-systolic LVP and the slope R (ms/mm Hg) of this relation was calculated. R quantified changes in τ, induced by the increase of end-systolic LVP during leg elevation and described afterload dependence of LVP fall



Correlation between changes were calculated using Pearson's correlation coefficient

Results: Response of rate of LV relaxation to increase in systolic pressures with leg elevation was related to the contractile response. An increase in dP/dt_{max} with leg elevation was associated with a low value of R, while a decrease in dP/dt_{max} was associated with a high value of R ($r = 0.88$; $p < 0.001$) (Figure 1). The effects on R and dP/dt_{max} during leg elevation were also closely related to the changes in EDP ($r = 0.80$; $p < 0.001$ and $r = 0.84$; $p < 0.001$ respectively)

Conclusion: These data demonstrated that response of contraction and relaxation were coupled during leg elevation in patients undergoing CABG. The magnitude in changes of EDP with leg elevation was indicative for the response of parameters of contraction and relaxation.

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A.196 Intrathoracic blood volume as a reliable cardiac preload indicator in mechanically ventilated PTS with PEEP

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Increased intrathoracic pressure, during positive pressure ventilation, reduces cardiac output (CO) because of a decrease in venous return. In mechanically ventilated patients, neither central venous pressure (CVP) nor capillary wedge pressure (PCWP), reflect cardiac preload accurately (1).

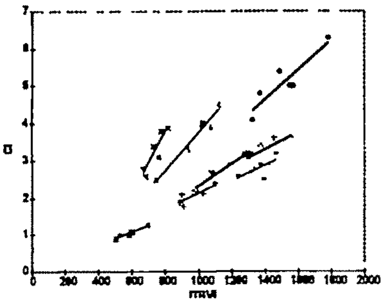
Goal of Study: to identify which of the two, CPV and intrathoracic blood volume (ITBV) better correlate to CO at different PEEP levels before and after an infusion of a determined volume of plasma expander

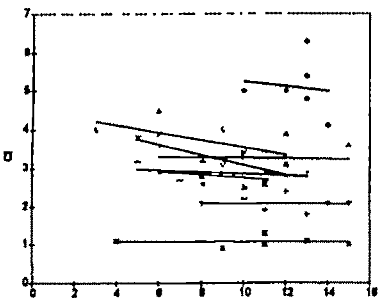
Material and Methods: in 8 surgical pts with stable hemodynamic conditions, CVP, ITBV index and cardiac index (CI) were measured at two different PEEP levels i.e. 10, 15 cmH_2O, before and after infusion of 500 ml of colloids. Measurement of ITBVI and CI were provided by the PiCCO system by means of a femoral arterial thermodilution catheter and an iced bolus with 15 ml of saline solution injected through a central venous line.

Results and Discussion: In our study, ITBVI and CVP were correlated to CI. The individual correlations coefficient (r) are illustrated in the following table:

Patient	1	2	3	4	5	6	7	8
CIvsITBVI	0 90	0 67	0.84	0.98	0 91	0 91	0.98	0 75
CIvsCVP	–0 71	–0 31	–0 03	–0 45	–0 19	–0 12	–0 20	–0 57

On average, correlation between CI and ITBVI was r = 0 70 (fig. a) and correlation between CI and CVP was r = –0.04 (fig. b).





To avoid CO decrease during mechanical ventilation (MV) is fundamental to assess actual cardiac preload. Both CVP and PCWP tend to increase during MV with PEEP in spite of a reduced venous return, thus they are not reliable preload indicators.

In our study the correlation between CI and CVP and between CI and ITBV were –0 04 and 0 70 respectively.

Conclusions: In mechanically ventilated pts with PEEP, ITBVI is a better cardiac preload indicator than CVP.

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A.197 Haemodynamic effects of an agonist of the vasopressin system for treatment of refractory hypotension at anaesthetic induction in patients on chronic ACEI-therapy: preliminary results

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Background: to determine the circulatory effects of terlipressine, an agonist of the vasopressin system, when used to counteract intraoperative hypotension in patients chronically treated by ACEI, when hypotension was refractory to conventional therapy with agonists of the sympathetic system.

Patients: twenty two patients, chronically treated with ACEI's, undergoing a peripheral vascular surgery were prospectively studied. A radial artery catheter was inserted prior to induction of anaesthesia

Methods: after an intravenous infusion of 10 ml/kg of Ringer's Lactate, propofol 1.5 mg/kg, sufentanil 0 5 mcg/kg and atracurium 0.5 mg/kg were given for induction. A transoesophageal echocardiography probe was used to assess left ventricular function (LVF). When systolic arterial pressure (SAP) became lower than 85 mmHg, a bolus of 6 mg of ephedrine or 100 mcg of phenylephrine was administered. This bolus was repeated two folds if SAP did not remain above 100 mmHg during 1 minute If this goal was still not obtained, we injected a bolus of 1 mg of terlipressine intravenously and haemodynamic parameters were recorded each 30 seconds during 6 minutes.

Results: hypotension was refractory to conventional vasopressor therapy in 6 of 22 patients. One minute after the injection of terlipressine the SAP increased from 83 ± 2 mmHg to 103 ± 10 mmHg. Peak value of SAP reached 119 ± 15 mmHg. This was not associated with change in fractional area change (0.57 ± 0.07 vs 0.54 ± 0.08) and heart rate (55 ± 4 vs 52 ± 4). Wall stress significantly increased from 39 ± 8 to 65 ± 15 (10^3 $dynes.cm^{-2}$)

No additional injection of vasopressor was needed during the perioperative period. No change in ST-segment was observed after the injection. Posperative diuresis was adequate in all cases

Conclusion: a bolus of 1 mg of terlipressine is effective to counteract intraoperative hypotension in patients chronically treated with ACEI who present hypotension refractory to conventional therapy.

A.198 A prospective, randomized comparison of haemodynamic behaviour and treated haemodynamic side effects during remifentanil/propofol/oxygen, remifentanil/desflurane/oxygen, remifentanil/sevoflurane/oxygen and alfentanil/isoflurane/nitrous oxide anaesthesia for ENT surgery

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Background and Goal of Study: The pharmacokinetics of remifentanil (REM), desflurane (DES), and sevoflurane (SEV) make them highly attractive for ENT-surgery. Accordingly, this study was to evaluate the haemodynamic behaviour and treated haemodynamic side effects of REM/propofol (PRO), REM/DES, REM/SEV and alfentanil/isoflurane/N_2O/O_2 (control [CONTR]) anaesthesia.

Materials and Methods: Following approval by the local Ethics Committee, 120 patients were randomly assigned to either REM/PRO, REM/DES, REM/SEV or CONTR anaesthesia (n = 30 each). Blood pressure was determined non-invasively before anaesthesia, before and 1 and 5 min after intubation, before and 5 min after start of surgery, and at, and 1 and 5 min after extubation. Low mean arterial pressure (MAP, <60 mmHg) and heart rate (HR, $<50\ min^{-1}$) for >3 min were treated with either atropine or etilefrine Data were statistically analyzed by ANOVA (for repeated measures where indicated), and by χ^2 and Fisher's exact test (significance level $p < 0.05$).

Results and Discussion: Patient characteristics were comparable between groups. Following induction of anaesthesia, MAP and HR decreased most in the REM groups (Table 1). There was no haemodynamic response to intubation in these groups. More patients receiving REM/PRO and REM/SEV required treatment for hypotension and/or bradycardia when compared to the REM/DES and CONTR groups (Table 2).

A 198 Table 1 Penoperative Haemodynamics (values are means ± SD)

	REM/PRO		REM/DES		REM/SEV		CONTR	
	MAP (mmHg)	HR (min^{-1})	MAP (mmHg)	HR (min^{-1})	MAP (mmHg)	HR (min^{-1})	MAP (mmHg)	HR (min^{-1}
bl	98 ± 16	74 ± 14	97 ± 17	74 ± 13	103 ± 14	70 ± 15	96 ± 17	71 ± 13
b i	63 ± 9†	58 ± 8†	76 ± 14†	63 ± 12†	77 ± 15†	62 ± 12†	81 ± 14†	69 ± 11
1′ a i	67 ± 10	58 ± 10	77 ± 15	64 ± 14	78 ± 19	66 ± 16	103 ± 21†	84 ± 14†
5′ a i	68 ± 9	54 ± 8	73 ± 10	62 ± 12	77 ± 12	60 ± 12	87 ± 17†	78 ± 12
b s	68 ± 9	54 ± 8	72 ± 10	59 ± 11	74 ± 10	57 ± 15	75 ± 11	66 ± 12†
5′ a s s	71 ± 12	59 ± 9	74 ± 12	60 ± 11	75 ± 11	59 ± 10	77 ± 16	62 ± 10
ext	89 ± 16†	68 ± 13*	96 ± 14†	82 ± 18†	98 ± 17†	81 ± 18†	106 ± 20†	98 ± 18†
1′ a e	97 ± 12	66 ± 11*	103 ± 17	79 ± 18	111 ± 15	81 ± 17	109 ± 17	88 ± 15
5′ a e	101 ± 12	68 ± 13*	106 ± 13	80 ± 14	108 ± 13	79 ± 13	103 ± 16	87 ± 17

bl = baseline, b i = before intubation, a i = after intubation, b s = before surgery, a s s = after start of surgery, ext = extubation, a e = after extubation, $^{*}p < 0\ 05$ vs other groups, $^{\dagger}P < 0\ 05$ vs preceding value

Table 2 Number of patients requiring treatment for haemodynamic alterations, n (%)

	REM/PRO	REM/DES	REM/SEV	CONTR
Induction	7 (23)	2 (7)	4 (13)	1 (3)
Intraop.	3 (10)	1 (3)	8 (27)	2 (7)
Total	10 (33)	3 (10)*	12 (40)	3 (10)*

Haemodynamic alterations hypotension and/or bradycardia * $p < 0\ 05$ vs REM/PRO and REM/SEV

Conclusion: Baseline anaesthesia with REM effectively blocks the stimulus of laryngoscopy, intubation and surgery Discontinuation of REM does not result in a reactive hyperdynamic response

A.199 Veno (inf. *vena cava*) – arterial carbon dioxide difference during clamping for surgery of the abdominal aorta

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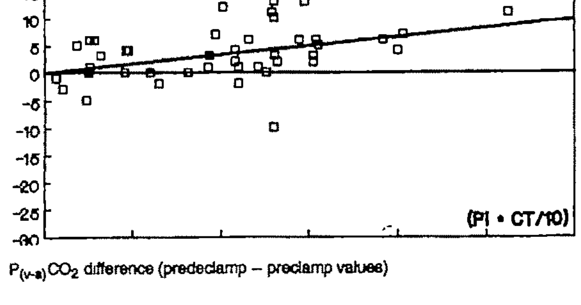
Quantitative increase in veno-arterial ΔPCO_2 has been observed in tissue dysoxia related situations. However, in a controlled animal setting, regional veno-arterial ΔPCO_2 ($P_{(v-a)}CO_2$) was increased only with ischemic and not with hypoxic hypoxia. During aortic clamping in humans the degree of peripheral ischemia is reversery related to the extend of the collateral circulation This study was aiming to investigate the relation of distal $P_{(v-a)}CO_2$ with the duration of the aortic occlusion (CT) and with the ankle-brachial pressure index (PI).

Material & Methods: After institutional protocol approval, 42 male patients (age: 66.4 ± 8.2, ASA I–III, EF > 40%) referred for elective infrarenal aortic surgery were studied Under continuous epidural combined with general anesthesia, 30 patients (Doppler mean bilat. PI = 0 94 ± 0.24) had aneurysm repair (AAA) with prosthetic tube graft, while in the rest (Doppler mean bilat. PI = 0 36 ± 0 14) repair was aiming to their occlusive disease (OD) of the difurcation Preoperatively, a heparinized inf v cava sampling line (via femoral) was introduced. Blood was transfused after data collection Patients were breathing $FiO_2 = 0.45$ and no hypoxic state was recorded during the procedure

Results: Total aortic occlusion in AAA (proximal + distal anastomoses) was 57 4 ± 12 0 min and 28 2 ± 9 2 in OD (only proximal) During clamping, $P_{(v-a)}CO_2$ was increased mainly in AAA (Table) The differences between pre-declamp and preclamp values of $P_{(v-a)}CO_2$ were correlated with PI, CT and product (PI * CT). Best correlation was found with the latter (fig), while it was positive with both PI (r = 0 371) and CT (r = 0 324) Although $P_{inf\ v\ c}CO_2$ remained elevated in the early declamping period, $P_{(v-a)}CO_2$ was decreased because of the systemic hypercarbia.

Discussion: The findings of this study and observations in animals concerning lower body tissue ischemic dysoxia are similar. Although distal venous CO_2 is increased, low flow from this part leads to decreased CO_2 load to the lungs during clamping[2] Difference in collateral vessels (reflected in PI) modifies the distal venous CO_2 augmentation



$P_{(v-a)}CO_2$ difference (predeclamp – preclamp values)

	Preclam	Pre-declamp	15′ after
AAA	5 56 ± 3 6	8 86 ± 4 3*	5 31 ± 3 7
OD	7 0 ± 3 3	8 43 ± 4 6	7 2 ± 3 2

$P_{(v-a)}CO_2$ values in mmHg, mean ± SD, * denotes $p < 0\ 05$ (t-paired)

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A.200 Cardiovascular and catecholamine responses to endovascular abdominal aortic aneurysm repair

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Background: Endovascular repair of abdominal aortic aneurysms (AAA) has been proposed as a less invasive alternative to conventional surgery, although there are few data to confirm this. We have compared haemodynamic, catecholamine and acid-base changes in patients undergoing endovascular or conventional AAA repair

Methods: 24 patients for AAA repair were divided into two equal groups, both received similar anaesthetic regimes Cardiovascular variables including cardiac index (CI), systemic vascular resistance index (SVRI), blood gases, plasma adrenaline and noradrenaline were measured prior to surgery, before, and 5 minutes after aortic clamping and clamp release (conventional) or occlusion & release (endovascular) and analysed by ANOVA and paired t-tests.

Results: (Mean (SEM))

Conventional	Baseline	Pre-xc	Post-xc	Pre-xc release	Post-xc release
CI ($l/min/m^2$)	2 9 (0 3)	3 4 (0 3)	3 4 (0 4)	3 4 (0 2)	3 5 (0 3)
SVRI (dyne s cm^{-5})	2420 (319)	1799 (155)	1654 (163)	1710 (146)	1718 (182)
pH	7 38 (0 01)	7 38 (0 01)	7 37 (0 01)	7 33 (0 01)	7 27* (0 1)
pCO_2(kPa)	5 2 (0 2)	5 2 (0 2)	4 9 (0 2)	5 2 (0 1)	6 1* (0 3)
BE	–0 9 (0 8)	–0 5 (0 4)	–1 5 (0 6)	–3 3 (0 6)	–5 2* (0 5)
Adr (pmol/ml)	1 5 (0 2)	3 2 (0 5)	2 8 (0 8)	2 9 (0 9)	2 6 (1 1)
NA (pmol/ml)	5 3 (0 6)	8 3 (1 3)	8 8 (1 3)	8 8 (1 5)	9 1 (1.6)

Endovascular	Baseline	Pre-occlusion	Post-occlusion	Pre-release	Post-release
C I ($l/min/m^2$)	2 7 (0 2)	2 9 (0 3)	3 2 (0 3)	3 1 (0 2)	2 9 (0 2)
SVRI (dyne s cm^{-5})	2373 (198)	2010 (234)	1759 (951)	1911 (165)	1925 (151)
pH	7 41 (0 01)	7 42 (0 01)	7 40 (0 02)	7 37 (0 02)	7 36† (0 1)
pCO_2 (kPa)	5 3 (0 3)	4 9 (0 2)	4 9 (0 3)	5.1 (0 3)	5 0† (0 2)
BE	0 4 (0 4)	–0 1 (0 4)	–1 2 (0 7)	–2 1 (0 7)	–2 2† (0 7)
Adr (pmol/ml)	1 1 (0 3)	1.0† (0 2)	0 7† (0 2)	0 7† (0.1)	0 7† (0 2)
NA (pmol/ml)	4.4 (0 9)	5 5 (1 3)	7 2 (1 4)	8 3 (1 5)	8 7 (1 4)

$^{*}p < 0\ 05$ compared with pre-xc, $^{\dagger}p < 0\ 05$ between groups

Discussion: There was a significant metabolic acidosis and increase in p_aCO_2 at aortic unclamping in the conventional group, but no parallel changes in the endovascular group. Changes in cardiac output were less than previously reported[1], which may be related to anaesthetic technique

Conclusion: Cardiovascular variables were stable in the endovascular group, and plasma adrenaline concentrations significantly lower compared to the conventional group

References

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A.201 Effects of dobutamine on haemodynamic changes during surgical procedures performed in the genupectoral position. An echo-Doppler study

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Background and Goal of Study: In the anaesthetized patients the genu-pectoral position has been associated with a marked decrease of the cardiac output and $etCO_2$ and a sharp increase of the systemic vascular resistences (1). This cardiovascular effect compromising tissue perfusion, can come to fearsome effects during the perioperative period (2) The use of low-invasive continuous haemodynamic monitoring offers information allowing an early diagnose and therapeutic intervention of cardiovascular alterations (1, 3). The study aim was to evaluate the cardiovascular effects of the genu-pectoral position during infusion of dobutamine.

Materials and Methods: Only patients in ASA1 class undergoing scheduled lumbar discal surgery were involved in the study, after informed signed consent, and were treated with the same anaesthetic protocol The dobutamine was given by continuous infusion at a rate of 3 μg/Kg/min, commencing 10 min before the induction of anaesthesia. Anaesthesia was induced with Fentanyl (1 μg/Kg), Propofol (1–2 mg/Kg) and Vecuronium bromide (0.12 mg/Kg) Anaesthesia was maintained with Isoflurane (<1 MAC) in N_2O-O_2 (50:50) and Fentanyl 1 μg/Kg/h After the induction, with the patients still lying in the supine position, an echodoppler probe (Dynemo 3000) was inserted via the nose into the oesophagus This device includes a 5 MHz pulsed doppler and a 10 MHz M-mode imaging system synchronized and able to measure simultaneously and continuously both blood flow velocity in the thoracic aorta and aortic diameter. Monitoring included the ECG, $etCO_2$, SpO_2, aortic blood flow (ABF), aortic stroke volume (SVa), aortic total systemic vascular resistences (TSVRa), mean arterial pressure (MAP), HR, aortic diameter, pre-ejection period index (PEPi), left ventricular ejection time index (LVETi) and the PEP/LVET ratio. Three sets of continuous measurements were then averaged (in supine, kneeling, and risupine position) Data recorded during the three periods were analyzed with the Anova test. A $p < 0.05$ was considered statistically significant

Results and Discussion: Twelve consecutive patients were enrolled into the study The cardiovascular changes by knee-chest position comparing to supine position are illustrated in table n 1.

Table 1 Haemodynamic variables * supine vs genupect

Parameter	Supine	Genupect	Risupine	P value
ABF	4.89 ± 0.6	3.09 ± 0.6	3.5 ± 0.5	0.01*
MAP	83 ± 18	86 ± 15	87 ± 8	n.s
HR	81 ± 9	79 ± 9	79 ± 7	n.s
SVa	49 ± 11	39 ± 7	44 ± 10	0.03*
TSVRa	1817 ± 258	2228 ± 389	2201 ± 244	0.002*
PEPi	150 ± 16	142 ± 6	139 ± 7	n.s
LVETi	413 ± 33	388 ± 62	404 ± 18	n.s
PEP/LVET	0.37 ± 0.07	0.36 ± 0.05	0.33 ± 0.02	n.s.
$etCO_2$ KPa	4.48 ± 0.2	4.32 ± 0.2	4.11 ± 0.3	n.s
Diameter	27.3 ± 2.8	27.4 ± 2.9	27.3 ± 2.9	n.s

There was a statistically significant decrease of the ABF and the SVa and increase of the TSVRa in the genu-pectoral position without reduction of myocardial contractility, as indicated by the stability of both the PEPi and the PEP/LVET. No changes were observed in regard to MAP, HR, $etCO_2$ and therefore tissue perfusion.

Conclusion: Transoesophageal echodoppler could detect reductions of the ABF not otherwise detectable. Dobutamine seems to have beneficial effects on the preservation of ABF and tissue perfusion

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A.202 Is load dependence of left ventricular relaxation influenced by β-adrenergic tone in coronary surgery patients?

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Background: Left ventricular (LV) relaxation rate in the failing heart is more dependent on systolic load than in the normal heart (1) The present study evaluated whether this dependence of rate of relaxation on LV pressures could be altered by β-adrenergic medication in patients undergoing coronary surgery (CABG).

Methods: Two groups of 10 patients with preoperative ejection fraction >40% were included. LV pressures were measured with a tipmanometer inserted in the LV cavity. Paced heart rate was 90 beats/min. LV pressures were recorded during leg elevation, resulting in an increase of LV pressures. The effects of leg elevation on LV contraction were evaluated by the changes in dP/dt_{max} Effects on LV relaxation were evaluated by the changes in the time constant τ of isovolumic relaxation. τ was linearly fit to the corresponding end-systolic LVP and the slope R (ms/mm Hg) of this relation was calculated R quantified changes in τ, induced by the increase of end-systolic LVP during leg elevation and described afterload dependence of LVP fall. In group 1, leg elevation was performed at baseline (*B*) and after administration of esmolol (*E*) 1 mg/kg (β-blocking agent). In group 2, leg elevation was performed at baseline and during administration of dobutamine (*D*) 5 μg/kg/min (β-stimulation). Correlations were calculated using Pearson's correlation coefficient. Comparison of slope and intercept of regression lines was performed using Student t-test

Results: A close relationship was observed between changes in dP/dt_{max} and changes in R in all conditions In group 1, dP/dt_{max} increased less after *E* and R was higher (0.315 ± 0.132 ms/mmHg at *B* and 0.816 ± 0.153 ms/mm Hg after *E* ($p < 0.001$)) Slopes and intercepts were not different, indicating that the individual values shifted along the same relation (Fig. 1) In group 2, dP/dt_{max} increased more during *D* and R was 0.039 ± 0.052 ms/mm Hg at *B* and 0.455 ± 0.149 respectively during *D*. Slopes and intercepts were not different, indicating that the individual values also shifted along the same relation (Fig. 2)

Fig 1

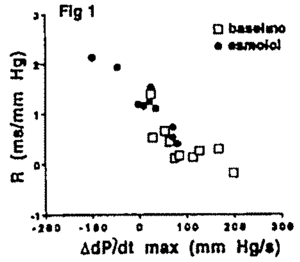
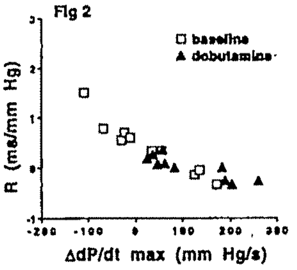


Fig 2



Conclusion: **E** increases, whereas **D** decreases load-dependency of LV relaxation. This change occurred along the same relationship, indicating that contraction and relaxation remained coupled

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A.203 A second post-induction dose of propofol does not attenuate the haemodynamic responses to intubation

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Background & Goal of Study: An EEG arousal reaction occurs during laryngoscopy and intubation which may be caused by a subcortical nociceptive input [1]. This can produce rises in heart rate and arterial pressure, resulting in myocardial ischaemia or infarction in susceptible patients. The aim of this study was to determine if a second bolus dose of propofol given immediately before laryngoscopy might attenuate these responses

Material & Methods: Twenty-six ASA 1&2 adult patients undergoing elective surgery requiring general anaesthesia and controlled ventilation were studied. Anaesthesia was induced with propofol 2 mg/kg and atracurium 0.6 mg/kg Patients were manually ventilated with isoflurane 0.8% and nitrous oxide 66% in oxygen. Two minutes after induction, patients received either propofol (Group P, n = 13) 1 mg/kg or intralipid 10% 0.1 ml/kg (Group C, n = 13).

Laryngoscopy and intubation was then performed. Heart rate (HR) and mean arterial pressure (MP) were recorded· (a) Before induction of anaesthesia (PR); (b) one minute after induction (PO), (c) one, three, five and ten minutes after intubation (1, 3, 5&10). Mean (SD) was calculated. Differences between groups (GR) were determined using unpaired 't' tests.

Results & Discussion: Both groups were comparable for age, weight and sex ratio HR and MP were similar in both groups before and after induction of anaesthesia. HR was significantly higher in the ten-minute period after intubation in Group P compared with Group C. There was no difference in MP between groups during this period.

GR	HR PR	HR PO	HR1	HR3	HR5	HR10
P	88 (21)	88 (17)	117** (12)	112** (10)	110** (12)	100** (13)
C	80 (19)	82 (13)	98 (12)	93 (12)	89 (12)	79 (13)
GR	MP PR	MP PO	MP1	MP3	MP5	MP10
P	90 (13)	81 (12)	98 (13)	83 (13)	80 (11)	73 (12)
C	98 (14)	83 (10)	102 (13)	88 (13)	84 (13)	77 (9)

Significant differences, * $p < 0.05$, ** $p < 0.01$

Conclusion: Surprisingly, the results show that a second post-intubation bolus dose of propofol 1 mg/kg produces an undesirable tachycardia following tracheal intubation.

References

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A.204 Minimum dose of esmolol which attenuates the chronotropic response to intubation

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Background & Goal of Study: Rises in heart rate occur following laryngoscopy and tracheal intubation which may result in myocardial ischaemia or infarction in susceptible patients. Esmolol, a short-acting beta-adrenoceptor antagonist, has been shown to suppress these responses (1) The aim of this study was to determine the minimum dose of esmolol required for this purpose.

Material & Methods: Fifty-two ASA 1&2 adults undergoing elective surgery requiring general anaesthesia and controlled ventilation were studied Anaesthesia was induced with thiopentone 4 mg/kg and atracurium 0.6 mg/kg, and maintained with isoflurane 0.8% and nitrous oxide 66% in oxygen. Two minutes after induction, patients received either saline 10 ml (Group S, n = 11), esmolol 1 mg/kg (Group E1, n = 10), esmolol 2 mg/kg (Group E2, n = 10), esmolol 3 mg/kg (Group E3, n = 11), or esmolol 4 mg/kg (Group E4, n = 10). Two minutes later, laryngoscopy and intubation was performed Heart rate (HR) was recorded (a) Before induction of anaesthesia (PR), (b) one minute after induction (PO); (c) one, three, five and ten minutes after intubation (1, 3, 5&10) Mean (SD) was calculated Differences between Group S and other groups were determined using multiple unpaired 't' tests

Results & Discussion: All groups (GR) were comparable for age, weight and sex ratio. The HR was similar in all groups before and after induction of anaesthesia The HR was significantly lower for one minute after intubation in Group E1, for ten minutes in Group E3, and for three minutes in Group E4 than the HR in Group S.

GR	HR PR	HR PO	HR1	HR3	HR5	HR10
S	82 (20)	89 (19)	102 (15)	98 (15)	87 (17)	82 (17)
E1	77 (13)	82 (14)	89* (13)	85 (11)	80 (12)	77 (10)
E2	86 (15)	91 (9)	98 (11)	94 (11)	90 (11)	85 (8)
E3	79 (14)	87 (16)	82** (10)	76** (11)	72* (12)	69* (13)
E4	81 (14)	95 (7)	89* (8)	84* (12)	80 (11)	82 (10)

Significant differences, * p < 0 05, ** p < 0 01

Conclusion: A minimum of 1 mg/kg of esmolol is required to attenuate the chronotropic response to intubation.

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A.205 Effects of halothane, isoflurane anaesthesia and magnesium infusion on heart rate variability

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Background and Goal of Study: Heart rate variability (HRV) became a quantitative method showing the activity of autonomic nerve system High frequency (HF) is thought to be controlled by parasympathetic nervous system while low frequency (LF) by the interaction of sympathetic and parasympathetic nervous systems, and the LF/HF ratio to be a marker of sympathovagal balance (1). HRV reducing effect of different anaesthetics has been investigated (2). Magnesium (Mg) is known to have a positive effect on autonomic nervous system instability (3) We investigated the effects of halothane, isoflurane anaesthesia and Mg infusion on HRV.

Materials and Methods: Forty-one patients (pts) (23 male, ASA physical status I–II) 25–45 years of age, undergoing general anaesthesia for elective orthopedic surgery were included in this study The pts with the diseases and receiving medication that had an effect on HRV were excluded The pts were evaluated in four groups: In group I (no 12) anaesthesia induction was performed by halothane, in group II (no·11) Mg was being infused during halothane anaesthesia, in group III (no 10) isoflurane anaesthesia was given and in group IV (no:8) pts received Mg during isoflurane anaesthesia. Power spectral analysis was done with high definition program using fast Fourier transformation in LF and HF bands. The LF/HF ratios were calculated by dividing LF to HF values Statistical analysis was done with paired student's t-test.

Results and Discussion: Mean arterial pressure significantly decreased during anaesthesia induction in all groups while there was no significant change in heart rate during the study. In groups I and II, LF, HF and the LF/HF ratio significantly reduced by anaesthesia induction. In groups III and IV, although LF and HF reduced significantly by induction, the LF/HF ratio did not change significantly. During maintenance of anaesthesia significant reduction in LF and HF values continued in all groups, also the LF/HF ratio decreased significantly in all groups except group III. The reduced HRV values increased to baseline in a shorter time during the recovery period in groups III and IV HF values increased significantly with Mg infusion only during surgical incision in group II.

Conclusions: Isoflurane anaesthesia which did not cause a significant change in the LF/HF ratio had an advantage in respect of preserving sympathovagal balance and having a shorter recovery period. Mg infusion had no significant effect on HRV.

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A.206 Heart rate variability: monitoring of autonomic nervous system activity during general anaesthesia

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Background: The monitoring of the heart rate variability (HRV) is a new, non-invasive method of the autonomic nervous system activity assessment LF (low frequency, 0.055–0 09 Hz) is an index of adrenergic activation, HF (high frequency, 0.1–0 4 Hz) is an index of cholinergic activation and TD (total density, 0.0033–0 5 Hz) is an index of total autonomic activity

Goal of Study: To examine changes in adrenergic and cholinergic activity during general anaesthesia by intraoperative HRV monitoring

Material & Methods: 21 patients, 17–72 years old (mean 40 5) without cardiovascular disturbances, who underwent operations on the facial cranium due to neoplasmic changes were anaesthetised using thiopental and suxamethonium for induction and nitrous oxide with fentanyl for maintenance of anaesthesia. HRV indexes were calculated from 5-minutes fragments of recorded ECG in Del Mar® Avionics Holter Analysis Systems software. To estimate the level of statistical significance t-Student's test was used.

Results: We observed the decrease of LF, HF and TD values during maintaining of anaesthesia and an intensive increase of LF and TD values during extubation of patients (see table, the difference between preoperative value.

Examined period of anaesthesia	LF [ms^2/Hz]	HF [ms^2/Hz]	TD [ms^2/Hz]
Before the operation	346 4	1350 1	5794 8
During induction and intubation	342 5	564 6	4560 5
After intubation	42 8***	136 7**	4142 7
During the operation	22 3***	46 2**	1112 3**
During deduction	187 1	616 4	8260 9
During extubation	1433 6*	3130 1	19911 6**
5 minutes after extubation	592 4	1603 9	17182 3

*p < 0 05, **p < 0 01, ***p < 0 001

Discussion: The decrease of autonomic system activity during maintaining of anaesthesia could be a consequence of nitrous oxide inhalation and barbiturates and opioids injections Increase of HRV indexes during extubation depends on mechanical trauma and anticholinesterase drugs injected during deduction of anaesthesia

Conclusions: Induction and maintenance of general anaesthesia suppress the autonomic system activity Extubation is followed by strong activation of autonomic nervous system

A.207 Effect of sandostatin on heart rate variability during anaesthesia and surgery

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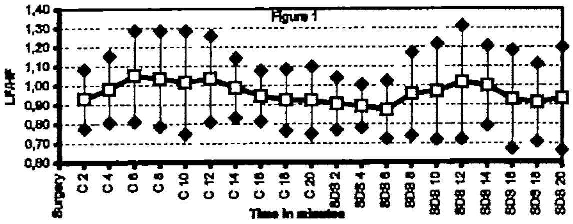
Background and Goal of Study: Heart Rate Variability (HRV) monitors the fluctuations of autonomic nervous system outflow to the heart as well as the balance between it's components (sympathetic and parasympathetic).[1] Intravenous Sandostatin (SDS, an analogue of the neuropeptide somatostatin) has been reported to produce transient bradycardia followed by systemic and pulmonary hypertension of very short duration [2] This study attempts to enlighten the mechanisms of this effect in humans during anaesthesia and surgery by power spectral analysis of Heart Rate Variability.

Materials & Methods: With the approval of the hospital's Ethical Committee, 10 patients who were to undergo surgery under total intravenous anaesthesia (TIVA) supplemented by nitrous oxide, entered the protocol of this study after signing informed consent All patients were of good physical status (ASA I), aged between 18–50 years A Holter machine was attached to the patients before induction to anaesthesia for subsequent off line HRV analysis They received TIVA with propofol (after Robert's scheme) and sufentanil infusions (0 5 μg/kg/min), cis-atracurium for muscle relaxation and mechanical ventilation with 60% nitrous oxide in O_2 (TV 8 ml/kg, RR. 15 bpm) After surgery begun, and anaesthesia was deep enough to accomplish stable haemodynamics for at least 10 minutes, a control recording of 20 minutes was marked on the Holter recording. By the end of this period, every patient received a slow bolus intravenous infusion of SDS 3.5 μg/kg in 20 ml normal saline. A second 20 minutes test period was marked on the Holter recording. During these 40 minutes, heart rate (HR), systolic (SAP) and diastolic (DAP) blood pressures were recorded manually. Statistical analysis was performed by using one way or two way ANOVA tests as required.

Results & Discussion: After SDS administration a statistically significant bradycardia was recorded ($p < 0.05$) followed by an increase in arterial pressure ($p < 0.05$) Meanwhile, HRV indices ratio (LF/HF, Figure 1, values are in mean ± SD, C = Control period, SDS = Sandostatin) did not change significantly, indicating no change of autonomic tone balance. Probably SDS activates somatostatin receptors in the heart and the peripheral and central vasculature or other reflex mechanisms that in either case do not affect autonomic nervous system balance.



Conclusions: Intravenous administration of Sandostatin during anaesthesia and surgery produces significant haemodynamic alterations without affecting the autonomic nervous system as expressed in Heart Rate Variability power spectral analysis.

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A.208 Autoregulation of inner ear blood flow during propofol and isoflurane anaesthesia in middle ear surgery

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Background and Goal of the Study: Controlled hypotension was used to have a bloodless cavity during middle ear surgery under optic microscope. No study assessed the effect of controlled hypotension on the inner ear blood flow (IEF) in humans IEF autoregulation was described in several studies (1) As isoflurane impaired cerebral blood flow autoregulation, we hypothesized that isoflurane impaired IEF autoregulation. The purpose of this study was to compare the effect of isoflurane on IEF autoregulation to propofol during controlled hypotension in 20 patients ASA 1

Method: After approval from the Institutional Ethics Committee and written informed consent, patients were randomly divided in two groups to receive either propofol or isoflurane Anaesthesia was induced with alfentanyl 0.03 mg kg^{-1} and propofol 3.5 mg kg^{-1} and tracheal intubation was performed. Then the anaesthesia was either propofol (9 mg kg^{-1} h^{-1}) or isoflurane (end-expiratory concentration adjusted to 0 9–1.1%) with alfentanyl (0 01 mg.kg^{-1}.h^{-1}) IEF and mean arterial pressure (MAP) were measured continuously. IEF was measured by laser Doppler flowmetry (2) Controlled hypotension was realized by the infusion of sodium nitroprusside (0 21 ± 0.04 mg.kg^{-1} h^{-1}) to decrease MAP by 20–50%. To quantify autoregulatory aspect of IEF responses to hypotension, a coefficient of autoregulation (G_a) was calculated. A G_a value of 1 implies perfect autoregulation.

Results: The patients characteristics did not differ significantly among the 2 groups. During controlled hypotension, MAP decreased by 50 ± 3% in propofol anaesthesia and by 58 ± 3% in isoflurane anaesthesia without difference between the group. The coefficient of autoregulation Ga was significantly higher during propofol anaesthesia (0.62 ± 0.03) than during isoflurane anaesthesia (0 22 ± 0.03, $P < 0.0001$).

Conclusion: To sum up, isoflurane has a greater propensity than propofol to decrease the capacity of the inner ear to maintain blood flow autoregulation during controlled hypotension in middle ear surgery Further studies are needed to explore the auditory consequences of IEF autoregulatory capacity loss during controlled hypotension in middle ear surgery.

Acknowledgements: "Hospices Civils de Lyon", HCL/P/95065

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A.209 Descending limb of the Frank-Starling curve: reality or myth?

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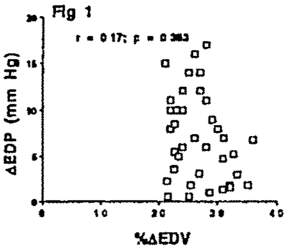
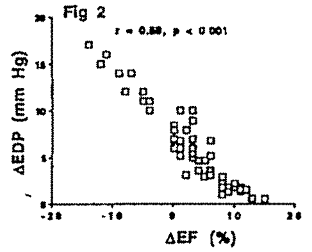
Background: Existence of the Frank-Starling mechanism in the failing human heart is a point of debate (1, 2). Especially, the presence of the descending limb is not accepted in clinical pathophysiology (3) The present study evaluated the Frank-Starling mechanism in anesthetized patients during coronary surgery (CABG).

Methods: Patients ($n = 50$) with preoperative ejection fraction >40% were included. LV pressures were measured with a fluid-filled catheter inserted in the LV cavity. A transesophageal ultrasound probe was positioned at the midpapillary level. Paced heart rate was 90 beats/min. LV pressures and echocardiographic images were recorded during leg elevation, which enhanced venous return to the heart and increased preload. Hemodynamic data, echocardiographic volumes and ejection fraction (EF) were analyzed before and at the end of leg elevation. Correlations were calculated using Pearson's correlation coefficient.

Results: Leg elevation induced a homogenuous increase in end-diastolic volume (EDV) The increase in end-diastolic pressure (EDP) was highly variable and unrelated to the increase in EDV (Fig 1) ($r = 0.17$, $p = 0\ 363$) The changes in EDP induced by leg elevation were not related to baseline values of EDP ($r = 0\ 32$, $p = 0.135$). A close inverse relationship was observed between changes in EDP and changes in EF ($r = 0\ 89$; $p < 0.001$). Patients with a limited increase in EDP showed an increase in EF. Patients with a marked increase in EDP showed no change or even a decrease in EF (Fig 2) A similar inverse relationship was shown between changes in EDP and changes in dP/dtmax ($r = 0\ 841$; $p < 0.001$)





Conclusions: The present findings indicate that patients undergoing CABG could be both on the ascending but also on the descending limb of the Frank-Starling curve A position on the descending limb was not due to impaired baseline diastolic function. Further research will have to elucidate if this phenomenon is due to impaired contraction-relaxation coupling and impaired contractility or to preload-induced diastolic dysfunction

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A.210 A comparison of the effects on heart rate and blood pressure during and after anaesthesia with induced hypotension using glyceryl trinitrate alone or labetalol alone

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Introduction: Glyceryl Trinitrate (GTN) given to induce hypotension during anaesthesia may cause an increase in heart rate (HR) [1], and labetalol given during surgery induces slowing of HR, which continues into the recovery period [2] The clinical relevance of these assertions were tested during anaesthesia with induced hypotension for tympanoplasty.

Methods: With patient consent and Ethical Committee approval 54 healthy adults were randomised to receive GTN or labetalol Anaesthesia was strictly standardised from premedication, through maintenance with isoflurane 2% and controlled ventilation to tracheal extubation After induction of anaesthesia, hypotension (mean arterial pressure [MAP] 50 to 65 mmHg) was induced with either GTN IV infusion (50 mgs in 500 mls dextrose saline) or labetalol IV injection (1 mg.kg^{-1}) augmented during surgery, if necessary, with esmolol (2.0 mg.kg^{-1}) or GTN (0.01 mg kg^{-1}), respectively HR/SAP was recorded before induction, after induction, every 15 mins during surgery and every 5 mins during recovery. Analysis used

ANOVA, Chi^2 and 't' tests ($p < 0.05$ significance). Mean values of all preoperative (N_1) HR's and SAP's were compared with all intraoperative (N_2) and recovery (N_3) recordings

Results: Test groups (N = 27 each) were comparable. During surgery HR/MAP were reduced by both agents, but more so with labetalol

	Preoperative			Intraoperative			Recovery		
	N_1	HR	MAP	N_2	HR	MAP	N_3	HR	MAP
GTN	27	87	93	129	79*	65*	176	90	79*
Lab	27	88	92	133	69*	58*	186	74*	79*
p	–	ns	ns	–	<0 001	<0 001	–	ns	<0 001

* < 0 001 versus preoperative mean Data given as mean

During recovery, HR returned to preoperative levels with GTN but remained slower with labetalol; MAP was the same in both groups.

Conclusion: Hypotension induced using GTN infusion is not accompanied by clinically relevant change in HR during or after surgery. Hypotension induced with labetalol during surgery does not persist during recovery, and is not accompanied by clinically relevant bradycardia during or after surgery

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A.211 Influence of dantrolene sodium on myocardial reperfusion injury after regional ischaemia in the rabbit heart *in vivo*

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Background & Goal of Study: Dantrolene sodium is a direct muscle relaxant which reduces calcium release from sarcoplasmic reticulum in skeletal muscles Intracellular calcium overload during ischaemia or reperfusion constitutes a primary cause of myocardial reperfusion injury. In isolated rat hearts, dantrolene sodium offered small protective effects against myocardial reperfusion injury (1) The aim of the present study was to investigate whether dantrolene sodium can reduce myocardial reperfusion injury after regional myocardial ischaemia in the rabbit heart *in vivo*

Materials and Methods: Eighteen chloralose-anaesthetized rabbits were subjected to 30 min occlusion and 180 min reperfusion of a major coronary artery. Left ventricular pressure (LVP, tip-manometer), cardiac output (CO, ultrasonic flowprobe), and infarct size (triphenyltetrazolium staining) were determined During the last five minutes of ischaemia, nine rabbits received 10 mg/kg dantrolene sodium intravenously (DAN). Another nine rabbits received the vehicle (DMSO) and served as controls (CON) Statistical analysis was done by Student's *t*-test.

Results: Baseline values were similar between groups (CON vs DAN: LVP, 99 ± 6 (mean ± SEM) vs 91 ± 6 mm Hg, P = 0.29, CO, 252 ± 26 vs 275 ± 23 ml min^{-1} P = 0.53). During coronary artery occlusion, LVP and CO were reduced to a similar extent in both groups (CON· LVP, 89 ± 3% of baseline values; CO, 90 ± 5%). After infusion of dantrolene sodium or the vehicle, there was a transient increase in CO to 108–113% of baseline values during the first 15 min of reperfusion. LVP did not recover to baseline values during reperfusion in both groups (CON vs DAN after 3 h 51 ± 5% vs 67 ± 7% of baseline, P = 0.10). Infarct size was 41 ± 4% of the area at risk in controls compared with 37 ± 6% in dantrolene sodium treated hearts (P = 0 59)

Conclusion: Dantrolene sodium does not attenuate myocardial reperfusion injury after regional myocardial ischaemia in the rabbit heart *in vivo*, when given at a clinically relevant concentration

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A.212 Effect of propofol on reperfusion injury in the isolated rat heart

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Background and Goal of Study: Intracellular calcium level and free oxygen radicals play an important role in development of myocardial reperfusion injury The intravenous anaesthetic propofol inhibits calcium influx across plasma membranes as well as calcium release from the sarcoplasmic reticulum (1), and is known to scavenge free oxygen radicals (2). Therefore, we investigated the effects of propofol on reperfusion injury in the isolated rat heart

Material and Methods: Isovolumetric beating rat hearts were retrogradely perfused (Krebs-Ringer solution) at a constant pressure of 100 cm H_2O Heart rate was kept constant at 370 beats min^{-1}. The left anterior descending coronary artery (LAD) was occluded for 30 min and reperfused for 2 h. In the treatment group, propofol dissolved in intralipid was added to the perfusate during the last 5 min of occlusion and the first 15 min of reperfusion period in order to achieve a final concentration of 1 μg propofol and 1 μl intralipid per ml perfusate In a second group, only intralipid, the vehicle of propofol, was added A third group served as untreated controls (each group n = 12) We measured left ventricular developed pressure (LVDP), dP/dt, and coronary flow (CF). Infarct size (IS) was determined by triphenyltetrazoliumchloride staining. Statistics were performed by ANOVA followed by Dunnett's post hoc test

Results: Baseline values of LVDP (129 ± 4 mmHg, mean ± SEM), dP/dt_{max} (4228 ± 139 mmHg s^{-1}), and CF (12 2 ± 0 3 ml min^{-1}) were similar in all groups LAD occlusion reduced LVDP to 28 ± 2%, dP/dt_{max} to 38 ± 2%, and CF to 45 ± 2% of baseline values During reperfusion, the values recovered to 77 ± 3%, 78 ± 3%, and 97 ± 2%, respectively. There were no differences in haemodynamics between the three groups during occlusion and reperfusion. Propofol had no effect on IS when compared with the intralipid group (25 0 ± 3 7% *vs* 26 9 ± 3 3% of the area at risk, P = 0.89). However, when compared with the untreated controls, IS in the intralipid group tended to be smaller (26.9 ± 3 3% *vs* 34 8 ± 3.2%, P = 0.19)

Conclusion: Given at a clinically relevant concentration, propofol provides no protective effect on myocardial reperfusion injury in rat heart *in vitro* Intralipid might have a small cardioprotective effect during reperfusion, possibly by an oxygen radical scavenging effect (2)

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A.213 Influence of inhalational anaesthetics on myocardial reperfusion injury after cardioplegic arrest in the isolated rat heart

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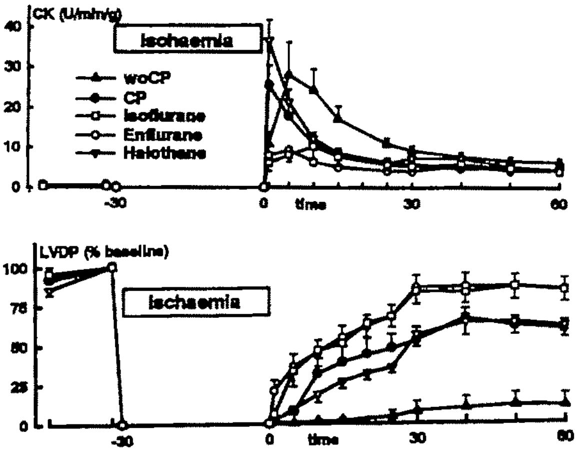
Background & Goal of Study: Previous studies have demonstrated that inhalational anaesthetics can protect against myocardial reperfusion injury in vitro as well as in vivo The aim of the present study was to investigate whether halothane, enflurane and isoflurane offer additional protection when given during reperfusion after cardioplegic arrest (CP)

Materials and Methods: Using a Langendorff-preparation, isovolumetric beating rat hearts were perfused with a modified Krebs-Ringer solution (KRS) at a constant flow (11 ml/min) and paced at a rate of 370 beats per minute. Left ventricular developed pressure (LVDP) and creatine kinase release (CKR) were determined as indices of myocardial performance and cellular injury, respectively. After cardioplegic arrest (2 min Bretschneider-cardioplegia, 2 ml/min), the hearts underwent 30 min of warm ischaemia (38.5°C), followed by 60 min of reperfusion In the treatment groups (each n = 9), a saturated solution of either halothane, enflurane, or isoflurane in KRS was infused during the first 30 min of reperfusion in a concentration equivalent to 1.5 MAC in rats 9 additional hearts underwent the same protocol without inhalational anaesthetic (CP), 7 hearts underwent the protocol without cardioplegia and without anaesthetics (woCP) Statistical analysis was done by ANOVA followed by Dunnett's test as post hoc test

Results:



Conclusion: Enflurane and isoflurane improved functional recovery and reduced CK release even after myocardial protection by cardioplegia, while in halothane treated hearts, CK release and functional impairment were similar to controls The differences between the substances suggest different mechanisms of protection.

A.214 Hyperoxic lung injury and lung free radical metabolism in rats; the effects of N-acetylcysteine

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Background and Goal of Study: Oxygen free radicals released during hyperoxia may contribute to lung injury The aim of this study was to investigate the relation between hyperoxic condition and lung free radical metabolism and to establish a possible protective role of N-acetylcysteine (NAC) against to this condition.

Materials and Methods: All the experimental procedures were reviewed and approved by the animal care and use committee of the institution. Twenty-eight male adult wistor rats were used in the study. Rats divided into four groups. Oxygen (100%) was given to animals for 24 hours for three days. Animals were treated with 1 mg/kg p o NAC for three days All the rats were anesthetized with 90 mg/kg ketamine. The lung tissues were taken for biochemical and histo-pathological examinations Catalase (CAT) glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), activities were measured As a peroxidation index, the malondialdehyde (MDA) concentration was determined Also, light microscopy were performed. As for statistical analysis Mann Whitney-U test was used. $P < 0.05$ was considered statistically significant

Results and Discussion: CAT activity was higher in the oxygen, NAS and oxygen + NAS groups than in controls ($p < 0\ 05$) There was not any significant difference between mean activity values of the GSH-Px enzymes. SOD activity was lower in the oxygen group than in control group ($p < 0.05$). There were, however no significant difference in SOD activities of control group and of NAS, NAS + 02 groups. MDA concentrations of NAS and NAS + 02 groups were higher than 02 and control group ($p < 0.05$). There were no significant difference in MDA concentration of 02 group and of control group. Light microscopy indicated structural changes in the lung cells of oxygen, NAS and also NAS + oxygen groups compared with control group. CAT, GSH-Px and SOD are the primary intracellular, antioxidant defense mechanism to cope with oxidant stress (1). It is possible that NAC could scavenge the active oxygen species directly by nonenzymatic reduction (2). The Interaction of NAC with 02 or OH would lead to the formation of N-acetylcysteine disulfide, with the intermediate formation of the thiyl radical The significance and reactivity of such a radical is unknown (3) Our results showed that NAC + 02 increased malondialdehyde levels in the lung tissues. The increase in catalase activity may occur as a compensatory mechanism against increased free radical metabolism.

Conclusion: It is concluded that NAC treatment cannot be used safely in the preventation of peroxidative damage caused by oxygen.

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A.215 Effects of isoflurane and halothane on hepatic blood flow and sinusoidal microcirculation in the presence of hypoxia

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Background and Goal of the Study: The effect of volatile anaesthetics on liver blood flow has been reported controversially In the literature In addition, the influence of hypoxia on liver macro- and microcirculation under inhalational anaesthesia is not completely understood Therefore, the purpose of the present study was 1) to examine the effects of isoflurane (ISO) and halothane (HAL) on hepatic blood flow at different concentrations in the presence of hypoxia and 2) to investigate hepatic sinusoidal microcirculation during inhalational anesthesia.

Methods: Female Sprague-Dawley rats (n = 6 per group, b.w. 255 ± 62 g) were anaesthetized with pentobarbital and ketamine. After tracheostomy rats were ventilated artificially with O_2 enriched air. Carotid artery and jugular vein were cannulated for blood pressure (MAP) monitoring, blood gas analysis and infusion. Ultrasound flow probes were placed around the aortic arch (cardiac output = CO), portal vein (PVF) and hepatic artery (HAF). Liver surface was observed by videomicroscopy and velocity of FITC labeled RBC was evaluated offline. Protocol ISO and HAL 0.5, 1.0, 1.5, and 2.0 MAC in normoxia (P_aO_2 126 ± 33 mmHg) and hypoxia (53 ± 11 mmHg). Data analysis was performed by one way ANOVA with Fisher's post hoc test ($p < 0\ 05$) and Student's T-test as applicable.

Results and Discussion: In ISO the relative portion of HAF from CO tended to decrease with increasing MAC in normoxia whereas the relative portion of PVF and total hepatic flow (THF) from CO remained unchanged RBC sinusoidal velocity showed no significant changes with different MAC in normoxia or hypoxia In ISO absolute values of hepatic blood flow remained unchanged in both normoxia and hypoxia but in HAL hepatic blood flow decreased dose dependently and except for HAF in hypoxia they were significantly different from value at 0 MAC and significantly lower as compared with those in ISO Percent changes of RBC velocity from 0 MAC were similar at 1 5 MAC in both normoxia and hypoxia of ISO (−25 0%). But at 1.5 MAC in HAL it was significantly lower in hypoxia compared with normoxia (−55.7% versus −32 9%) and in hypoxia it was significantly lower in HAL than that of ISO

Conclusion: ISO preserves hepatic macro- and microcirculation as compared with HAL both in normoxia and hypoxia.

A.216 Tissue of oxygen extraction during ketamine anaesthesia in dogs: effects of sympathetic blockade

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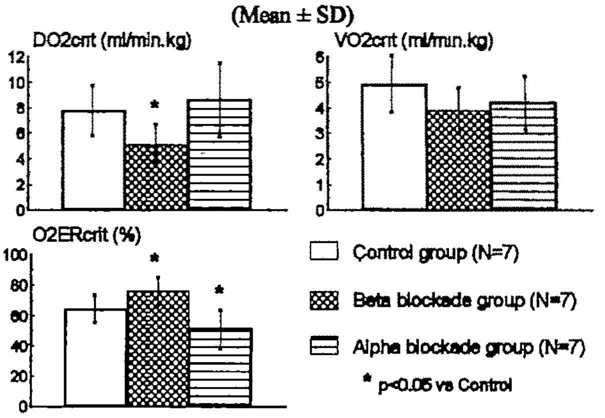
Background and Goal of Study: We tested the hypothesis that sympathetic blockade, and more precisely alpha adrenergic blockade will decrease tissue O2 extraction capabilities during haemorrhage in ketamine anaesthetized dogs

Material and Methods: Twenty-one mongrel dogs (25.5 ± 3.7 kg) were anaesthetized with ketamine (5 mg/kg + 0 2 mg/kg.min) and pancuronium (0 1 mg/kg + 2 mg/h) and mechanically ventilated with air (PaCO2 35–40 mmHg). 30 min after splenectomy, the animals were randomized in three groups. Dogs received IV propranolol (2 mg/kg) in the first group (Beta group; N = 7); IV phenoxybenzamine (3 mg/kg) in the second group (Alpha group; N = 7), or served as control in the last group (Control group, N = 7) 30 min after administration of the studied medication, dogs were progressively haemorrhaged by successive withdrawals of 5 ml/kg of blood At each step, Oxygen delivery (DO2) and oxygen consumption (VO2) were measured after a 10 min period to achieve a new steady-state. VO2 was directly measured using an infrared CO2 analyzer and a paramagnetic O2 analyzer DO2 was calculated from thermodilution cardiac output and arterial O2 content. In each dog, critical DO2 (DO2crit) and VO2 (VO2crit) were obtained from a plot of VO2 vs DO2, as the point of intersection of the two best fit regression lines determined by a least sum of squares technique (1) Critical 02 extraction (O2ERcrit) was the ratio of VO2crit on DO2crit. Data obtained at critical point were compared using a one way analysis of variance, followed when indicated by a Tukey HSD test.

Result:



Conclusions: In the conditions of our study alpha adrenergic blockade is associated with a decrease in tissue O2 extraction capabilities, while beta adrenergic blockade is associated with an increase in tissue O2 extraction capabilities

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A.217 Depressive effect of alfentanil on isolated human atrial muscle

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Background and Goal of Study: The synthetic narcotic alfentanil have been used widely in anaesthesia, because cardiovascular stability can be maintained with in the high doses However it has been observed that alfentanil caused transient cardiac stimulation in intact dog and (+) inotropic and (−) chronotropic effect in isolated rabbit heart. Clinically bradycardia or sinus arrest could be appeared by fentanyl-derived analgesics which has been attributed to increased vagal tone The purpose of this study was to define the direct effects of alfentanil on the isolated human atrial muscle.

Materials and Methods: This study was approved by the Hospital Ethical Committee. Atrial tissues from seven male patients during coronary artery bypass operation were studied All patients received similar anaesthetic and anaesthesia was induced using fentanyl and diazepam with pancuronium and maintained using fentanyl and pancuronium During atrial canulation a small piece of the atrial tissue was removed and stored in cold solution and immediately transported to the laboratory. None of the patients received inotropic support before the atrial tissue was removed. Atrial tissue was cut strip (1–2 mm wide and 8–10 mm long) and suspended in organ bath containing Krebs solution at 37°C and gassed with 95% O_2 and 5% CO_2 mixture and isometric contractions were recorded The atrial strip was stimulated electrically with a square-wave DC impulse at 1 ms duration and 1 Hz.

Results and Discussion: Alfentanil caused concentration-dependent inhibition of contraction of isolated human atrial strips

Alfentanil (M)	10^{-10}	10^{-9}	10^{-8}	10^{-7}	10^{-6}	10^{-5}	10^{-4}
% Contraction (mean)	95 8	89 5	86 1	84 6	68 8	63 1	50 1
S E M	3 9	4 6	6 6	8 3	13 8	14 7	20 4

This study showed that alfentanil in high concentration caused depression of cardiac contraction in human heart

Conclusion: It could be suggested that adjustment of anaesthetic dose of the alfentanil in clinic application is very important and application of the high dose alfentanil should be avoided

A.218 Effects of midazolam and flumazenil in isolated rabbit hearts

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Background: Midazolam, a short acting benzodiazepine, can cause an increase or decrease in contractile force of myocardium in a dose dependent manner (1) The goal of our study was to determine the effects of midazolam on contractile response and heart rate of isolated rabbit hearts and to investigate the reversal effect of flumazenil, a benzodiazepine antagonist

Materials and Methods: Isolated New Zealand rabbit hearts ($n = 5$ in each group) were perfused with Krebs Henseleit Bicarbonate buffer solution at a constant pressure of 55 mmHg according to the Langendorff method The heart rate (HR) and left ventricular pressure (LVP) were measured throughout a balloon inserted into the left ventricle and recorded via a pressure transducer After a stabilization period, hearts were perfused with midazolam with increasing concentrations of 0.5 to 50 μM (1 to 100 fold more than the clinically relevant concentrations respectively) After a 10 minute incubation period for each midazolam concentration, flumazenil (0.025 and 0.05 mg min^{-1}) was infused for 10 minutes concurrently with midazolam perfusion. A flumazenil infusion alone had no effect in LVP and HRs ($p > 0.05$) The statistical analysis was done by using ANOVA and student's t test

Results and Discussion: The 5, 10, 20, and 50 μM midazolam decreased LVP (13 4 ± 2 2, 18.9 ± 5 4, 33.6 ± 3 1 and 35.6 ± 4.7% of baseline, respectively) significantly ($p < 0\ 05$). HRs were also decreased with the concentrations of 10, 20 and 50 μM midazolam (13 1 ± 2 6, 20 1 ± 3 5 and 24 6 ± 3 2% of baseline respectively, $p < 0.05$) Flumazenil infusions had no effect on midazolam-induced decrease in LVP and HRs

Conclusions: Midazolam developed a dose related myocardial depressant effect in the isolated rabbit heart model However, these effects may not have been observed on LVP and HR in clinically relevant doses in humans Additionally, flumazenil had no reversal effect of midazolam-induced cardiac depression indicating that cardiac depressant effect of midazolam may not be via benzodiazepine receptors.

Acknowledgements: Supported by Roche Company, Turkey.

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A.219 Myocardial effects of desflurane in hamsters with cardiomyopathy

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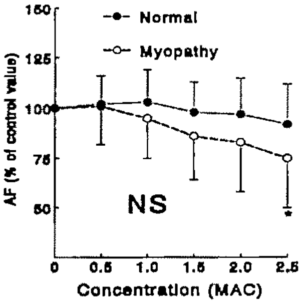
Background: The effects of desflurane on myocardial contraction and relaxation in diseased myocardium have not been completely understood

Material and Methods: The effects of equi-anesthetic concentrations of desflurane (0 5 to 2 5 MAC) on inotropy (isometric active force, AF) and lusitropy in left ventricular papillary muscles of normal and cardiomyopathic (strain BIO 14.6) hamsters were investigated *in vitro* (29°C, pH 7 40, Ca^{2+} 2 5 mM, stimulation frequency 3/min). Data are mean % of baseline ± SD.

Results: Desflurane had no significant inotropic effect in normal hamsters (AF at 2.5 MAC. 92 4 ± 20%, NS) In cardiomyopathic hamsters, desflurane induced a moderate negative inotropic effect (AF at 2 5 MAC 75 ± 25%, $P < 0.05$) Nevertheless, there was no significant difference between the two groups (Figure) After α- and β-adrenoceptor blockade or pretreatment with reserpine, the inotropic effect of desflurane was not significantly modified. This result contrast with that previously observed in the rat myocardium (1). In both strains, desflurane induced no lusitropic effect under low load or under high load



Conclusion: The myocardial effects of desflurane were not significantly different in normal and cardiomyopathic hamsters

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A.220 Ischaemic preconditioning and tissue noradrenaline concentration in the rat heart

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Background: Ischemic preconditioning (IP) provides a significant cardioprotective effect against ischemic injury. Because the release of noradrenaline (NA) from sympathetic nerve endings during ischemia plays an important role in the extent of ischemic injury, we investigated the relation between the effect of IP and tissue NA level in the rat heart

Methods: The effect of IP, which is elicited by 3 cycles of 5 min of left coronary artery occlusion, was evaluated by comparing the infarct size of the myocardium with the area at risk after a subsequent 30 min of ischemia and 60 min of reperfusion The tissue concentration of NA in the left ventricle, the intraventricular septum, and the right ventricle during sustained ischemia was determined by using an HPLC-electrochemical detection The data from the infarct size and the NA concentration were analyzed by the Mann-Whitney test and the ANOVA with Bonferroni's adjustment, respectively

Results: IP reduced the infarct size (Con 56 ± 11% vs IP 16 ± 17%, Mean ± SD, $n = 6$, $P < 0\ 01$) The concentration of NA in the left ventricle gradually decreased after the onset of sustained ischemia, the effect being significant 60 min after ischemia (850 ± 66 ng/g before ischemia vs. 608 ± 117 ng/g 60 min after ischemia, Mean ± SD, $n = 6$, $P < 0\ 05$) The NA level in the right ventricle, in which ischemia was not induced, did not change during 60 min of ischemia Ischemic preconditioning did not exert an influence on the decrease of tissue NA level produced by 60 min of ischemia (Con 608 ± 117 ng/g vs. IP 597 ± 97 ng/g, Mean ± SD, $n = 6$, NS).

Conclusion: Ischemic preconditioning protected the heart in the histologic aspect, although it did not alter tissue NA level in the rat heart

A.221 Effects of hypertonic sodium solution in rat and rabbit myocardium: a mechanical and electrophysiological study

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Background and Goal of the Study: Hypertonic sodium media (HS) has been advocated in the treatement of haemorrhagic shock But its inotropic effects remain debatable.r The goal of this study was to compare the inotropic effects of HS in rat and rabbit myocardium.

Materials and Methods: Ventricular papillary muscles from rat (n = 7) and rabbit (n = 1) hearts were both isolated and studied at 29°C in Krebs-Henseleit solution Ca^{2+} was at 0 5 mM (rat) and 2.5 mM (rabbit) with Na^{+} at 140 mM. The mechanical parameters were obtained with stimulation at 0 2 Hz (rat) and 0.3 Hz (rabbit) the maximum unloaded shortening velocity (Vmax), the maximum active isometric force (AF), the contraction-relaxation coupling under isotonic (R1) and isometric (R2) conditions, reflecting respectively the sarcoplasmic reticulum (SR) and the calcium myofilament sensitivity Data are expressed as mean % of control value ± SD. Transmembrane resting (RP) and action (AP) potentials were recorded on both rat (n = 12) and (n = 9) rabbit papillary muscles using intracellular microelectrodes technique (resistance 15–20 MΩ; tip potential less than ± 3 mV).

Results and Discussion: HS induced a negative inotropic effect in the rat (AF: 75 ± 8%, Vmax· 90 ± 10%) and a positive ,inotropic effect in the rabbit (AF: 122 ± 22%, Vmax· 116 ± 22%) Nevertheless R1 and Ré remain unchanged HS shortened the plateau duration of rat muscle. In rat, total replacement of Ca^{2+} by Sr^{2+} is known to lengthen the plateau and the AP duration (APD). In the presence of Sr^{2+}, HS significantly lengthened the APD. In rabbit, HS prolonged the plateau duration and the repolarizing phase of the AP Despite opposite inotropic effect of HS in rat and rabbit, Ca^{2+} uptake by the SR and Ca^{2+} sensitivity myofilament were not altered. HS lengthened the AP duration in rabbit suggesting that the Ca^{2+} influx has been increased and induced a positive inotropic effect. In rat, HS shortened the plateau duration and exerted a negative inotropic effect. But, in presence of Sr^{2+}, HS induced a lenghtening of the AP duration of rat mimicking the rabbit AP. This suggested that HS increased the Ca^{2+}-activated K^{+} current in this preparation Such an increase migth lead to a reduction of the Ca^{2+} influx via voltage-dependent Ca^{2+} channels and account for the negative inotropic effect of HS in rat heart muscle

Conclusion: HS induce opposite inotropic effect according to rat and rabbit. These differences may be explained by the HS action on the influx of Ca^{2+} during the action potential. $^{2+}$ influx

A.222 Acute potassium ion replenishment normalizes arrhythmia rate in chronic hypokalaemic rats *in vitro*

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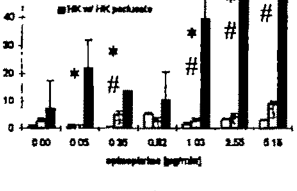
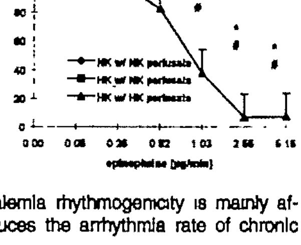
Chronic hypokalemia was shown to be a major risk factor for ventricular premature complexes[1]. Controversial is whether rapid K^{+} replenishment increases the risk of arrhythmia? Acute K^{+} replenishment on epinephrine induced arrhythmias was studied in isolated hearts of normal and chronic hypokalemic rats.

Methods: With IRB approval, isolated hearts of Sprague-Dawley rats (n = 6 per group) on [K^{+}]-free diet >3 weeks were perfused with hypokalemic ([K^{+}] 2 0 mM, HK-HK) or normokalemic ([K^{+}] 4.5 mM, HK-NK) Krebs solution. A normally fed control group was perfused with normokalemic (NK-NK) Krebs solution The hearts were mounted in a modified Langendorff-preparation with a leftventricular balloon (preload 2–12 mmHg, coronary perfusion pressure 70 mmHg/37°C). After equilibration, epinephrine was infused at 0.05, 0 25, 0.515, 1.03, 2.55 and 5 15 µg/min for 3 min each. Intraventricular pressure and heart rate were recorded. Posthoc the time of arrhythmias >5 sec duration was determined. For statistics, U-test by Mann and Whitney was used.

Results and Discussion: Serum [K^{+}] in chronic hypokalemic animals was significantly lowered ([K^{+}] 2.14 vs. 3.98 mM). Intraventricular pressures were 84–95 mmHg In hypokalemic hearts, the arrhythmia rate increased significantly with epinephrine and hypokalemic perfusate; it did not differ from normokalemic rats when perfused with normokalemic solution

Chronic hypokalemic rats have an increased disposition for major arrhythmias Acute K^{+} replenishment to 4.5 mM reduces arrhythmias to normal





Conclusion: With chronic hypokalemia rhythmogenicity is mainly affected. Acute K^{+} replenishment reduces the arrhythmia rate of chronic hypokalemic rat hearts to normal.

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A.223 Haemodynamic effects of inhaled nitric oxide and intravenous milrinone in cardiac surgical patients with pulmonary hypertension

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Background and Goals of Study: Inhaled nitric oxide (NO) produces selective pulmonary vasodilation in cardiac surgical patients with pulmonary hypertension (PH)[1] The aim of the study was to investigate the haemodynamic effects of inhaled NO and intravenous milrinone, a phosphodiesterase III inhibitor, in patients with PH before cardiac surgery.

Patients and Methods: We studied 16 cardiac surgical patients with PH scheduled for valvular replacement and/or myocardial revascularization. After induction of anaesthesia measurements included: mean blood pressure (MBP), mean pulmonary artery pressure (MPAP), right atrial pressure (RAP), pulmonary wedge pressure (PWP), continuous mixed venous saturation (SvO2) and cardiac output (CO). Systemic and pulmonary vascular resistances (SVR and PVR), stroke index (SI) and oxygen delivery (DO_2) were calculated by standard formulae. Patients were randomized in two groups: group I (NO): received 20 ppm of NO inhalation and group II (MIL): received 0 5 $\mu g.kg^{-1}.min^{-1}$ of i.v. milrinone Measurements were made at baseline (BAS) and after 20 minutes of NO inhalation or milrinone infusion

Results and Discussion: Both NO and milrinone caused a significant reduction on MPAP, but only NO was selective for pulmonary vessels Furthermore, NO produced a greater reduction on MPAP, (−22%) compared to milrinone (−14%)

	Group I		Group II	
	BAS	NO	BAS	MIL
MBP (mmHg)	87 (18)	82 (19)	75 (2)	71 (4)*
MPAP (mmHg)	37 (6)	29 (6)*	35 (5)	30 (3)*
RAP (mmHg)	14 (2)	13 (3)	15 (3)	14 (3)
PWP (mmHg)	24 (5)	19 (3)	24 (3)	21 (3)
CO ($L\ min^{-1}$)	3 12 (0 8)	3 43 (0 8)	2.99 (0 6)	3 28 (0.8)
SVR ($dyn\ sec\ cm^{-5}$)	1855 (653)	1597 (436)	1688 (389)	1468 (463)
PVR ($dyn\ sec\ cm^{-5}$)	361 (149)	235 (93)*	335 (107)	207 (94)*
SI ($mL\ m^2$)	30 (10)	30 (9)	28 (5)	31 (9)
SvO_2 (%)	70 (12)	69 (8)	72 (6)	71 (7)
DO_2 ($mL\ min^{-1}$)	511 (149)	626 (225)	406 (79)	407 (94)

Mean (SD), * $p < 0.05$ compared with BAS value, t-test

Conclusions: Inhaled NO is more efective and selective than milrinone for treatment of PH in cardiac surgical patients

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A.224 Demographic data of responders and non-responders to inhaled nitric oxide among patients with mitral valve stenosis

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Background and Goal of the Study: Inhaled nitric oxide (NO) is increasingly used to test the vasodilator capacity of the vascular bed in various groups of patients with pulmonary hypertension. This may also potentially apply to patients with mitral valve stenosis, therefore we decided to find out, whether a response to NO was related to the initial demographic data in this group of patients.

Materials and Methods: After ethical committee approval and informed consent, we studied 26 patients scheduled for mitral valve replacement due to mitral valve stenosis, with a mean pulmonary artery pressure (PAm) greater then 30 mmHg. Arterial line and pulmonary catheter were inserted in local anaesthesia and 30 ppm NO in 100% oxygen was given for 15 minutes during spontaneous ventilation via a tightfitting face mask before induction of anaesthesia. Patients with a decrease of a PAm > 10% entered a "responders" group (R), while those with a decrease of PAm < 10% entered "non responders" group (NR). Demographic data of these groups were compared (t-test and Pearson's two-tailed test).

Results and Discussion: 10 patients entered NR group and 16 entered R group. Mean PAm decrease was 17.1% (from 4.3% to 36 5%). Patients in NR group had significantly lower weight and were more frequently classified NYHA IV. Other factors were not found to be significantly different in these groups (see table).

	R (n = 16)	NR (n = 10)	Signf
Sex (M/F)	7/79	2/8	NS
NYHA (IV/III)	7/9	9/1	0 03
Reoperative (Y/N)	1/15	3/7	NS
Age (years)	54 7 ± 10 84	56 3 ± 8 56	NS
Height (cm)	167 ± 7 9	162 ± 5 5	NS
Weight (kg)	68 5 ± 10 9	58 1 ± 9 16	0 02

Conclusion: In patients with mitral stenosis and pulmonary hypertension, "non-responders" to NO have significantly lower weight and are more frequently in heart failure.

A.225 Expression of endothelin receptors in the pulmonary circulation

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Introduction: Until now, the distribution of the receptor subtypes mediating pulmonary vascular reactions of endothelin-1 is still unclear Some investigators described ETA receptors as the predominantly expressed subtype in the pulmonary circulation [1] whereas ET_B receptor related vasoconstriction has also been reported [2] Aim of our study was to investigate the receptor subtypes which are expressed in the pulmonary circulation of the rat using polymerase chain reaction

Methods and Results: The experiments were performed on isolated pulmonary arteries of 6 rats (SD). Total RNA was extracted according to the method described by Chomczynski [3]. First-strand cDNA was synthesized incubating RNA (6 μg) at 42°C for 60 min with a mixture (10 μl) of Superscript II reverse transcriptase, 5xRT buffer 0.1 M DTT, 50 μM poly dT_{16}, and 10 mM each dNTP (dATP, dCTP, dTTP, dGTP) Thereafter the mixture was incubated 15 min at 75°C to stop the reaction For the PCR amplification, an aliquot (0.5 ml) of RT product was mixed with 25 mM $MgCl_2$, 10x PCR buffer, 10 mM dNTP, 10 pmol/μl of each sense and antisense primer in a volume of 30 μl. 1 unit of Taq DNA polymerase was added using hot start PCR technique The thermal cycle profile (35 cycles) used in this study was 1) denaturing for 1 min at 94°C, 2) annealing primers at 55°C for 1 min, 3) extending the primers for 1.5 min at 72°C. The sequences of the primers were· ET_As 5′TTCGTCATGGTACCCTTCGA3′; ET_Aas 5′GATACTCGTTCCATTCATGG3′; ET_Bs 5′TTCACCTCA GCAG GATTCTG3′, ET_Bas 5′AGGTGTGGAAAGTTAGAACG3′. A portion (10 μl) of the PCR product was electrophoresed in a 1% agarose gel in TAE buffer. The gel was stained with ethidium bromide and photographed. The integrity of the cDNA preparation was shown by GAPDH controls. In each preparation both ET_A and ET_B receptors were detectable.

Conclusions: The present results demonstrate that ET_A and ET_B receptors are expressed in rat pulmonary arteries mediating endothelin effects

Acknowledgements: This study was supported by a grant from the Faculty of Clinical Medicine, Univ. of Heidelberg

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A.226 Effects of endothelin-1 in the pulmonary circulation

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Introduction: The effects of the vasoactive substance endothelin-1 (ET-1) in the pulmonary circulation are not completely understood. Pulmonary vasoconstriction [1] after ET-1 injection has been described but also vasodilation [2] Aim of the present study was to examine the effects of ET-1 in the isolated lung with respect to ET_A and ET_B receptor mediatled actions

Methods and Results: The experiments were performed on isolated rabbit lungs which were perfused with a cell and plasma free buffer solution The pulmonary arterial pressure (PAP) was continuously registered Intermittently perfusate samples were drawn to determine thromboxane A_2 (TXA_2) and prostacyclin (PGI_2) levels ET-1 injection (10^{-8} M, control; n = 6) resulted in an immediate increase in PAP (14.3 ± 0 8 mmHg at 20 min) which was followed by a second one 60 min thereafter leading to a final PAP of 28 6 ± 0.9 mmHg at 120 min The pressure reaction was paralleled by an increase in TXA_2 and PGI_2 levels. Pretreatment with the ET_A receptor antagonist LU135252 (10^{-6} M, n = 6) markedly reduced the PAP during the whole observation period ($p < 0.01$) and also reduced the generation of cyclooxygenase products ($p < 0.01$ at 30, 90 min, $p < 0\ 05$ at 120 min). In contrast to this, pretreatment with the ET_B receptor antagonist BQ788 (10^{-6} M, n = 6) amplified the immediate PAP increase after ET-1 injection (25 8 ± 1.1 mmHg after 20 min; $p < 0\ 01$ vs control) The PAP remained on this high level until the end of the observation period The generation of PGI_2 was reduced as compared to the other groups

Conclusions: The ET-1 induced vasoconstriction is mediated via the ET_A receptor subtype The generation of TXA_2 seems to play an essential role in the maintenance of the vascular reaction Since the blockage of ET_B receptors aggravates the PAP increase after ET-1 injection, it could be concluded that ET-1 limits his own vasoconstrictor effects by ET_B receptor related vasodilatory potency.

Acknowledgements: This study was supported by a grant from the Faculty of Clinical Medicine Mannheim, Univ of Heidelberg

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A.227 Effect of halogenated and intravenous anaesthesia on hypoxic pulmonary vasoconstriction and cyclo-oxygenase and nitricoxide-synthase blockade

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Aim: HPV is better preserved with intravenous than volatile anesthesia and is enhanced by COX and NOS blockade We wondered whether iv L-NA (L) 10 mg kg^{-1} (NOS inhibition) and indomethacin (I) 2 mg.kg^{-1} (COX inhibition) differently affect HPV under inhalational or intravenous anesthesia

Methods: 16 dogs were anethetized in random sequence with sevoflurane 1 MAC (H) and propofol (P) 18 mg $kg^{-1}.h^{-1}$, in hyperoxia (FiO2 0 4) and hypoxia (FiO2 0 1) before and after I + L. Pulmonary hemodynamics was studied by multipoint pulmonary artery-left atrial pressure (Ppa-Pla) over cardiac index Q relationships and impedance (PVZ) spectra obtained from Fourier series for instataneous Ppa and Q

Results: Ppa-Pla/Q plots and PVZ were identical at baseline and after (I + L). Hypoxia-induced upwards shifts of pressure (*) were increased by I + L (§) and more with P than H (°) ZO (0 Hz impedance) and 1^{st} modulus Z1 were increased with hypoxia (*) and futhermore with I + L (§) PVZ spectra were not differently affected by anaesthesia Table & Figure· mean ± SE $p \leq 0\ 05$; * hypoxia, ° anest, § I + L Fig Ppa-Pla/Q plots

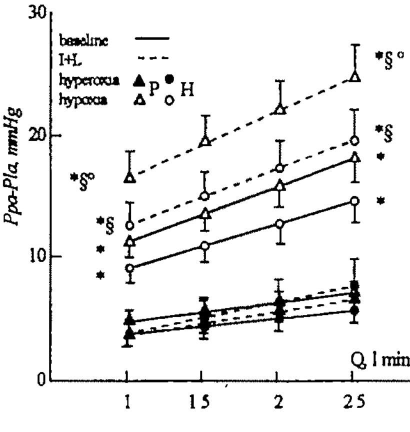

Table. ΔP (mmHg), Z0 and Z1 (dyn s cm^{-5}) at same Q

	I + L	Halogene		Propofol	
FIO2	0 4	0.1	0 4	0 1	
ΔP	before	6 ± 1	$14 \pm 2^{*}$	8 ± 1	$19 \pm 2^{*°}$
	after	6 ± 1	$17 \pm 2^{*§}$	6 ± 1	$25 \pm 3^{*§°}$
Z0	before	507 ± 38	$816 \pm 84^{*}$	518 ± 44	$834 \pm 7^{*}$
	after	859 ± 156	$1846 \pm 341^{*§}$	688 ± 93	$1480 \pm 232^{*§}$
Z1	before	58 ± 5	$92 \pm 10^{*}$	71 ± 8	100 ± 8
	after	85 ± 11	$148 \pm 19^{*§}$	84 ± 11	$152 \pm 19^{*§}$

Conclusion: In the intact dog, 1° basal pulmonary vascular tone is not modulated by I + L, 2° HPV is preserved with P and H, but attenuated with H, 3° HPV enhancement by I + L is maintained under P and H, but less with H and 4° hypoxia-induced increase in distal resistance and proximal elastance and/or wave reflection is increased with I + L

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A.228 Pulmonary vascular tone does not affect central blood volume

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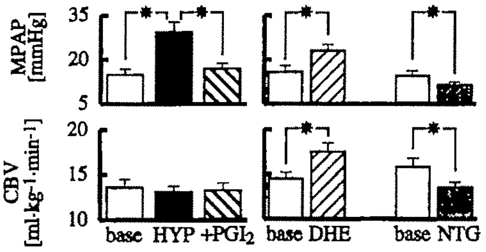
Background and Goal of Study: Most of the central blood volume (CBV) is held in non-contractile pulmonary vessels [1] Therefore, changes in pulmonary vascular tone should not be accompanied by changes in CBV To test this hypothesis we altered pulmonary vascular tone and systemic tone as well and measured CBV along with intravascular pressures

Materials and Methods: In 35 experiments on 5 anaesthetized (pentobarbitone) dogs we measured CBV as the product of cardiac output (thermodilution) and mean central transit time (Indocyanine green) The tracers were injected into the right atrium and the dilution curves recorded in the pulmonary artery and ascending aorta via fiberoptic thermistor probes. Transit times were calculated by deconvolution of the dye dilution curves [2]. Pulmonary vascular tone was altered by hypoxia (HYP, 10% O_2 in N_2) and aerosolized prostacyclin (PGI_2, 7.5 ng/kg.min), systemic vascular tone by dihydroergotamine (DHE, 7.5 μg/kg) or nitroglycerin (15 μg/kg min).

Results and Discussion: CBV remained constant despite marked changes in mean pulmonary arterial pressure (MPAP) during HYP and subsequent PGI_2 inhalation However, CBV followed the changes in MPAP induced by altering systemic vascular tone (fig. 1).



Means ± SEM ; * $p < 0.05$, t-Test, α-adjusted

Conclusion: Pulmonary vascular tone does not affect central blood volume, which however changes passively along with mean pulmonary arterial pressure when the blood distribution is altered by systemic vascular tone

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A.229 Carbon dioxide reactivity in patients with sleep apnoea syndrome: a transcranial Doppler study

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Background and Goal of Study: Patients with sleep apnoea syndrome (SAS) are known to be at greater long-term risk of stroke and transient ischaemic attacks[1] possibly due to impaired cerebral autoregulation. In normal patients, cerebral blood flow changes linearly by 20% per 1 kPa change in end-tidal CO_2 ($FE'CO_2$)[2] We have examined this phenomenon in patients with SAS

Materials and Methods: We studied nine patients aged 18–65 who were diagnosed with SAS according to standard clinical criteria and measured their baseline $FE'CO_2$, heart rate, mean arterial blood pressure and mean cerebral blood flow velocity (CBFV). The measurements were repeated after a 1 kPa change in baseline $FE'CO_2$ in either direction Hypercapnia was achieved breathing 2.5% CO_2 in oxygen and hypocapnia was obtained by voluntary hyperventilation. The results were analysed using the Wilcoxon Rank Sum test and Kruskal-Wallis test and those reaching statistical significance are shown below

Results and Discussion:

	Hypocapnia mean (SD)	Baseline mean (SD)	Hypercapnia mean (SD)
$Fe'CO_2$ (kPa)	4.04 (0 39)	5.10 (0.39)	6 26 (0 40)
CBFV (cm s^{-1})	41 18 (11.62)*	49 70 (10 96)	72.82 (16 20)*
% change in CBFV.kPa^{-1}	19.27 (7 38)*	–	43 08 (27 31)*
Wilcoxon Rank *p*	0 008	–	0 008

*$p < 0\ 05$

Conclusions: In patients with SAS, hypercapnia is associated with exaggerated CO_2 reactivity when compared with hypocapnia ($p < 0\ 012$). This may be an early indication of loss of cerebrovascular tone in this group of patients

Acknowledgements: Association of Anaesthetists of Great Britain and Ireland grant for the purchase of the SciMed QVL120 Doppler.

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A.230 Packed cell volume variations in a rabbit model of arterial thrombosis and bleeding

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Background and Goal of Study: Anaemia induces a lengthening of the bleeding time (BT). We have studied the role of haematocrit (Ht) variations in a Folts'model of experimental arterial thrombosis and bleeding

Material and Methods: 24 anaesthetised New Zealand rabbits were ventilated and continuously monitored for blood pressure, temperature, and carotid flow (electromagnetic flowmeter). Sequentially an injury and a stenosis (>60%) were carried out on the carotid artery, inducing thrombosis with cyclic flow reductions (CFR) recorded over a 20-min period. Animals were randomised into 3 groups. control (C), Platelet Rich Plasma (PRP) including a blood withdrawal (BW) followed by a compensation with rabbit homologous PRP, Whole Blood Retransfusion (WBR) including a BW substituted with a gelatin, followed by whole blood retransfusion At the beginning of the experiment and after each CFR period (CFR 1· before BW, CFR 2: after BW, CFR 3· after compensation with PRP or whole blood) blood samples (platelet count Pl, Ht, prothrombin time and fibrinogen), ear immersion BT and ex-vivo platelet aggregation test were performed At the end of the experiment, a laparotomy with a spleen section was done and the amount of wound bleeding (WB) was recorded. Data were expressed as mean ± SD except for CFR and WB (medians with extremes) – ANOVA

Results: In PRP and WBR groups, decrease in Ht abolished CFR, lengthened BT, and increased WB. Blood retransfusion in WBR group induced CFR reappearance, and BT shortening No change in prothrombin time or fibrinogen was observed

	C (n = 8)	PRP (n = 8)	WBR (n = 8)
CFR1 (n)	4 5 (3–6)	4.0 (3–10)	7 0 (3–13)
CFR2 (n)	4.0 (1–5)	0 0 (0–1)*	0 0 (0–0)*
CFR3 (n)	3 5 (0–6)	0 0 (0–1)*	4 0 (2–9)•
Ht 1 (%)	37 ± 4	36 ± 3	38 ± 3
Ht 2 (%)	36 ± 4	23 ± 2*	23 ± 2*
Ht 3 (%)	34 ± 3	22 ± 3*	31 ± 3•
Pl 1 (Giga/l)	243 ± 54	263 ± 82	317 ± 61
Pl 2 (Giga/l)	236 ± 60	235 ± 66	220 ± 66
Pl 3 (Giga/l)	211 ± 47	230 ± 65	240 ± 47
BT 1 (sec)	77 ± 25	76 ± 24	84 ± 37
BT 2 (sec)	76 ± 21	114 ± 36*	127 ± 29*
BT 3 (sec)	73 ± 28	118 ± 38*	114 ± 42*
WB (g)	6 (3–16)	9 (4–22)	13 (8–30)*

* $p < 0\ 05$ versus C-• $p < 0.05$ versus PRP

Conclusion: Decrease in Ht limits arterial thrombosis, and increases bleeding in the rabbit. Ht normalization induces a reappearance of thrombosis and BT shortening.

A.231 Intraoperative haemodynamic changes during open and laparoscopic adrenalectomy for phaeochromocytoma

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Introduction: Surgical treatment of non malignant adrenal disorders is increasingly performed under laparoscopic approach (2). Both pneumoperitoneum and adrenal tumor manipulation may induce haemodynamic (HD) variations The aim of this study is to compare the HD effects of laparoscopic or conventional surgery for phaeochromocytoma

Methods: Between january 93 and february 97, 22 patients undergoing surgery for phaeochromocytoma have been compared: 11 laparoscopic transabdominal adrenalectomies (LA); 11 open transabdominal adrenalectomies (OA). HD data were retrospectively collected for each patient by a radial arterial line and a Swan Ganz catheter; included heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), pulmonary capillary wedge pres-sure (PCWP) and cardiac index (CI) at 4 periods incision-insufflation (A), dissection (B); tumor excision (C), end of surgery (D). Systemic vascular resistances (SVR) and left ventricular work index (LVWI) were calculated. Maximal and minimal arterial systolic pressure (Max SAP, Min SAP) were recorded for each patient throughout the procedure Statistics: Student's t test (continuous data); chi-square test (qualitative data).

Results & Discussion: The 2 groups have no significant difference for: age, sex, size and side of the tumor, preoperative and intraoperative

A 231 Table

	A		B		C		D	
	LA	OA	LA	OA	LA	OA	LA	OA
HR bpm	72 ± 24	78 ± 19	94 ± 20	86 ± 21	90 ± 16	94 ± 26	87 ± 12	86 ± 21
MAP mmhg	105 ± 21*	86 ± 13	121 ± 32	114 ± 19	82 ± 10	78 ± 15	83 ± 15	84 ± 14
CVP mmhg	12 ± 4*	8 ± 3	14 ± 6*	8 ± 3	12 ± 6*	7 ± 3	10 ± 5	9 ± 2
PCWP mmhg	15 ± 3*	11 ± 4	20 ± 6*	12 ± 5	15 ± 7*	11 ± 2	13 ± 5	13 ± 6
CI 1/mn/m2	2 6 ± 1 3	3 1 ± 0 7	3 7 ± 1 3	3 9 ± 0 8	3 5 ± 0 9	4 ± 0 6	3 2 ± 1	3 7 ± 0 9
SVR dyn s/c m5	2442 ± 1212	2082 ± 786	1951 ± 1219	1805 ± 672	1315 ± 738	1264 ± 383	1156 ± 383	1493 ± 1418
LVWI g m/cm2	44 ± 22	48 ± 7	52 ± 15*	75 ± 23	39 ± 11	43 ± 14	40 ± 11	44 ± 12

* $p < 0\ 05$

used vasoactive drugs, blood volume expansion, urine output Results are shown in the tables.

	LA	OA
Max SAP mmHg	213 ± 23	215 ± 50
Min SAP mmHg	87 ± 14	86 ± 18

In LA group, significant HD variations are an increase of MAP (at incision period), CVP and PCWP (throughout all the laparoscopic period) Those variations have been reported by authors who studied HD in laparoscopic surgery (1) they are the circulatory response to pneumoperitoneum In fact, at the end of the procedure all the HD data are comparable in the 2 groups. We do not find any significant difference due to the tumor manipulation

Conclusion: This study shows that, for the HD standpoint, LA is an acceptable alternative to open adrenalectomy

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RESPIRATION

A.232 Gas exchange and intrapulmonary shunting during liver transplant

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Background: Up to now, severe hypoxemia is regarded as a contraindication for liver transplant (LTx) One of the causes of hypoxemia in cirrhotics is the so called hepatopulmonary syndrome (HPS) (defined as intrapulmonary vascular dilatations resulting in right-to-left shunting), that may reverse after LTx

Aim: To investigate pulmonary gas exchange during LTx and whether hypoxemic patients with HPS have a different postoperative course.

Patients and Methods: We studied 7 patients with HPS and 31 cirrhotic patients with normal PaO_2 (No-HPS) Arterial (a) and venous mixture (vm) blood gases were assessed after anesthetic induction; 20 min after breathing 100% O_2 and 20 min after breathing 21% O_2. We compared the postoperative time on mechanical ventilation, time on admission in ICU and number of pulmonary complications during postoperative period in both groups of patients. All data are presented as mean ± SEM Statistical analysis was performed using analysis of variance (ANOVA) with unpaired-t-test.

Results: Measurements of PaO_2, $PvmO_2$ and intrapulmonary shunt (Q_S/Q_T) were as follows·

	HPS		NO-HPS	
	21% O_2	100 O_2	21% O_2	100 O_2
PaO_2 (mmHg)	61 ± 19	437 ± 81$^+$	81 ± 19*	448 ± 109$^+$
$PvmO_2$ (mmHg)	41 ± 4	75 ± 5$^+$	39 ± 4	61 ± 10*$^+$
Q_S/Q_T (%)	51 ± 20	28 ± 9$^+$	23 ± 14*	27 ± 20

(* = $p < 0\ 05$ between 21–100% O_2, $^+$ = $p < 0\ 05$ between groups)

No differences between HPS and no-HPS were shown in postoperative time on mechanical ventilation (10 4 ± 9.5 *vs* 19 6 ± 18.1 hours) and time on admission in ICU (6 6 ± 0.9 *vs* 8 9 ± 6.7 days). No pulmonary complications were shown in HPS patients, whereas 5 patients without HPS presented complications (pneumonia: n = 4. and pleural effusion: n = 1).

Conclusions: Contrary to No-HPS, in HPS patients Q_S/Q_T decreases breathing 100% O_2 suggesting the presence of functional shunt. In HPS patients who have normal response to 100% O_2, the immediate postoperative evolution was not influenced by low PaO_2 before transplant. Accordingly, we suggest that hypoxemia due to HPS should not be *per se* a contraindication for LTx

Supported by grant Fis 95/0752

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A.233 Abrogation of pulmonary dysfunction induced by liver ischaemia-reperfusion: role of circulating xanthine oxidase

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Background and Goals of Study: We demonstrated the coexistence of lung dysfunction and no flow-reflow conditions in a different organ (Ref). We hypothesized that XO can be responsible for such damage This study aimed at substantiating this contention.

Materials and Methods: Male Wistar rat livers were isolated and perfused with oxygenated Krebs-Henseleit solution (KH), lungs from different rats were ventilated and perfused with KH + 5% bovine serum albumin After 30′ stabilization, livers were continually perfused (Control, n = 8), made globally ischemic (Ischemia, n = 8), or livers retrieved from rats pretreated with XO inhibitor sodium tungstate were also made ischemic (STG, n = 6) for 2 h This was followed by liver + lung 15′-reperfusion phase where the hepatic effluent was connected to the pulmonary circulation Livers were then disconnected and lungs only recirculated with the accumulated KH for another 45′.

Results and Discussion: Peak inspiratory pressure and static compliance decreased (fig 1-A, B) by 40% during lung reperfusion with Ischemia liver effluent, pulmonary vascular resistance also increased. Lungs of the Ischemia group showed a continuous weight gain up to 50% of baseline at 60′ reperfusion (fig. 2) These parameters remained unchanged in the Control and STG groups XO activity in the STG group perfusate was as low as in the Controls but far higher in the Ischemia group This suggests that XO is associated with acute lung injury and tungstate prevented it by preventing the production of XO

Figure 1

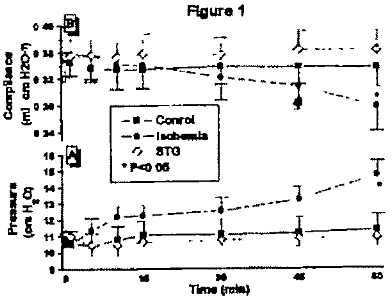
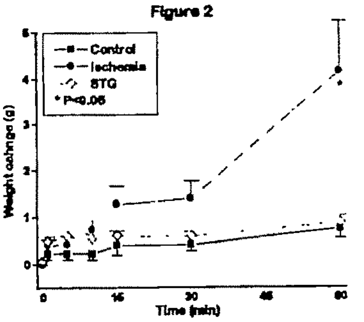


Figure 2



Conclusions: XO induces a direct lung dysfunction when the latter is exposed to compounds released from a different organ undergoing a post-ischemia reperfusion (e.g, liver) The mechanism(s) and location(s) by which XO and possibly oxygen species damage the remote organ functions remain to be further investigated.

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A.234 Re-expansion of atelectasis during general anaesthesia. A study using computed tomography

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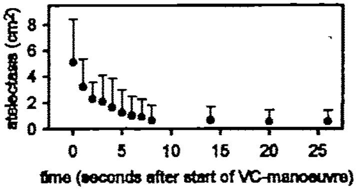
Background & Goal of Study: During general anaesthesia with mechanical ventilation, gas exchange is regularly impaired. A major cause of this derangement is atelectasis, causing pulmonary shunt [1]. Atelectasis may be re-expanded by a vital capacity (VC-) manoeuvre (i.e. an inflation of the lungs up to VC, kept for 15 seconds) [2]. This results in a decrease of pulmonary shunt and improved oxygenation [3]. However, such a manoeuvre might cause cardiovascular adverse effects. Reducing the time of maximal inflation to a few seconds will improve the margin of safety. The aim of the present study was to analyze the change over time in the amount of atelectasis *during* a VC-manoeuvre.

Material & Methods: A consecutive sample of 12 adults with healthy lungs, scheduled for elective surgery, was included in the study. Intravenous anaesthesia (Fentanyl, Propofol, Pancuronium) with controlled mechanical ventilation was used. For the VC-manoeuvre the lungs were inflated up to an airway pressure (P_{aw}) of 40 cmH$_2$O This pressure was kept for 25 seconds. Atelectasis was estimated by analysis of computed x-ray tomography [2] before and during the VC-manoeuvre

Results & Discussion: (Mean ± SD). The change in the amount of atelectasis over time is shown in the figure. PaO$_2$ increased from 16.9 ± 4.5 before to 21 6 ± 6.4 kPa ($P = 0.03$) after the VC-manoeuvre (FiO$_2$ = 0 4). PaCO$_2$ remained unchanged at 4.7 ± 0.6 kPa (VT = 9 ± 1 ml.kg^{-1}).



Conclusions: In anaesthetized, mechanically ventilated adults with healthy lungs, an inflation of the lungs to a P_{aw} of 40 cmH$_2$O, kept for 6–8 seconds only, may re-expand all previously collapsed lung tissue Thus, the previously proposed time for a VC manoeuvre may be halved in such subjects.

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A.235 Vital capacity manoeuvres after cardiopulmonary bypass. Effects on lung function in a pig model

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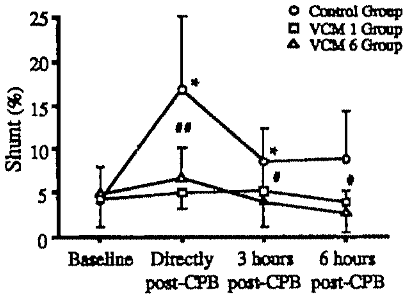
Background & Goal of Study: Respiratory failure after cardiopulmonary bypass (CPB) remains a major complication after cardiac surgery. In a recent study, using a pig model, we have shown that CPB generates a larger amount of atelectasis (35% of the total lung area) than a control group without CPB (2%) and that PaO$_2$ and intrapulmonary shunt correlated with the amount of atelectasis (1) We tested the benefit of a vital capacity manoeuvre (VCM) performed just before termination of bypass and if there is any advantage of repeating the VCM

Material & Method: 18 pigs received hypothermic CPB and were observed for 6 hours after CPB The VCM was performed in two groups and consisted in inflating the lungs during 15 seconds to 40 cmH$_2$O at the end of the bypass. In one of these groups the VCM was repeated after bypass every hour. The third group served as control Atelectasis was studied by computed tomography and extra vascular lung water (EVLW) by double indicator technique. Analysis for variance (ANOVA) with Bonferroni/Dunn as post hoc test was used.

Results: Intrapulmonary shunt increased after bypass in the Controls but not in the two VCM groups (Figure). Despite a spontaneous but limited improvement intrapulmonary shunt remained significantly lower in the two VCM groups at 3 and 6 hours after CPB. Six hours after CPB the control pigs showed significantly larger atelectasis than in the two other groups The only difference between the two VCM groups was a significantly higher compliance six hours after the end of the bypass in the group with a VCM performed every hour. The amount of EVLW did not increase after CPB in any groups.

Conclusions: In conclusion, a VCM performed at the end of the CPB protect against the increase in intrapulmonary shunt seen in the control group This protective effect of the VCM remains until 6 hours after bypass There is no extra benefit on gas exchange by repeating the VCM.



* $P < 0.05$ compared to baseline; # $P < 0.05$ and ## $P < 0.01$ between the two groups

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A.236 Does the prone position improve arterial oxygenation during non-invasive positive inspiratory pressure ventilation?

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Background & Goal of the Study: Beneficial effect of prone position in acute respiratory failure during conventional endotracheal tube ventilation is well known. The aim of the study was to evaluate effect of prone position on arterial oxygenation in the patients under ventilatory support with facial mask.

Materials & Methods: 17 patients with acute respiratory failure (ARF) in the early postoperative period after open heart surgery were studied. The causes of ARF were: ARDS on the stage of recovery, after extubation – 7, dyslectasis of basal segments of the lungs – 8, pneumonia – 2. The ventilatory support was carried out through Respironics facial mask and ventilatory modes employed were· Pressure Support – in 13 and SIMV + Pressure Support – in 4 patients The prone position ventilation was carried out with repeated periods of 30–40 min during prolonged noninvasive mask ventilation (NIMV).

Results of the study are presented in the table (M ± m).

Parameters	PaO$_2$	Qs/Qt	FiO$_2$/PaO$_2$
Units	mm Hg	%	–
Spontaneous	54 ± 15	7 4 ± 0 7	234 ± 30
NIMV	37 ± 42*	4 8 ± 0 6	234 ± 28*
NIMV in PP	101 ± 55*	3 6 ± 0 3*	306 ± 28*

FiO$_2$ = 0.21; PP – prone position, *$p < 0$ 05

Before NIMV, on spontaneous breathing, all patients manifested arterial hypoxemia with diminished values of FiO$_2$/PaO$_2$ and increased Qs/Qt NIMV followed by the significant improvement of arterial oxygenation. and this effect was augmented after turning the patients into the prone position The changes of PaCO$_2$ were not significant.

Conclusions: Prone position is an effective measure leading to further improvement of arterial oxygenation in the patients on the noninvasive mask ventilatory support. It can be recommended as an additional method of respiratory therapy in the patients with postoperative respiratory failure

A.237 Effects of reverse Trendelenburg on compliance and oxygenation indices in obese surgical patients

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Background and Goal of Study: Obese patients have several respiratory derangements during surgical procedures and anesthesia. The aim of this study was to evaluate the effects of position changes on respiratory system compliance and gas exchanges in obese patients during bariatric surgery.

Materials and Methods: 20 obese patients BMI > 47.9 ± 7.7 undergoing biliopancreatic diversion were studied. We satisfied the requirements of our institution regarding the use of human subjects in research. Protocol of anesthesia was standard and all patients were mechanically ventilated (Servoventilator 900 C) with· Tidal Volume 6–8 ml/Kg/Total Body Weight aiming to $EtCO_2$ of 30 mmHg, FiO_2 50% Patients were examined at standard times. T_1 after induction of anesthesia, T_2 after laparotomy T_3 after costosternal destructors position, T_4 in reverse Trendelenburg Respiratory system Compliance (C_{rs}) was computed by measuring airways pressures during inspiratory and expiratory holds (3 seconds), artery blood samples were collected for gas analysis at each time. Statistical analysis of data collected was performed employing Student's test ANOVA and regression analysis Data are presented as means ± Standard deviation

Results:

Times	T_1	T_2	T_3	T_4
$DAaO_2$	181 ± 115*	186 + 66	221 ± 68*	196 + 77
$PaO2/FiO_2$	3 4 ± 1 1	2 8 ± 1 2	2 3 ± 0 7	2 9 ± 1
Crs	31 ± 6	33 ± 5 5	33 ± 4 6$^{\$}$	42 ± 8 6$^{\$}$
Peak Paw	34 ± 7 3	31 ± 5 3	32 ± 2 9$^{\#}$	27 ± 3 5$^{\#}$
Plateau Paw	24 ± 5 5	24 ± 4 3	24 ± 3	20 ± 3 3
Mean Paw	9 8 ± 1 5	9 4 ± 2 3	9 2 ± 1 7	8 3 ± 2 8

Conclusions: In our series reverse Trendelenburg position determines a significant improvement of compliance and a decrease in airways pressures Nevertheless this position determines a bit, but non statistically significant improvement of oxygenation indexes It's likely that a change of regional ventilation/perfusion matching could offset the increase of compliance and hence of Functional Residual Capacity as suggested by other authors (1)

References

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A.238 Effects of fentanyl and alfentanil on breathing pattern during halogenated anaesthesia

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Background & Goal of Study: Halogenated anaesthetics and opiates have different depressant effects on ventilatory control[(1)]. We compared the breathing pattern during halothane (HAL) or isoflurane (ISO) anaesthesia at 1 2 MAC and after the addition of fentanyl (FEN) or alfentanil (ALF)

Material & Methods: After institutional approval and informed consent, 40 patients undergoing surgery were enrolled Subjects received 1.2 MAC of HAL or ISO in O_2. When breathing was stabilized, flow and end-tidal CO_2 pressure ($PETCO_2$) were recorded. Afterwards, a single equipotent dose of FEN (1 $\mu g.kg^{-1}$) or ALF (6 $\mu g\ kg^{-1}$) was given and measurements were repeated again five minutes later. Breathing pattern was analyzed in terms of inspiratory time (TI), inspiratory to total time ratio (TI/TTOT), respiratory rate (RR), tidal volume (VT), minute ventilation (VE) and mean inspiratory flow rate (VT/TI) Statistical analysis was performed by MANOVA with significance considered at $p < 0.05$

Results & Discussion: ISO depresses ventilation more than HAL. When opiates were added, RR and VE were thus markedly reduced and $PETCO_2$ increased, despite a moderate increase in VT. FEN reduced VE more than ALF, however, VT/TI remained the same.

	Halogenated		Halogenated + opiate	
	HAL	ISO	FEN	ALF
TI (s)	0 98 ± 0 17	1.01 ± 0 19	1 42 ± 0 22	1 31 ± 0 27
TI/TTOT	0.44 ± 0 03	0 43 ± 0 04	0 23 ± 0 10	0 30 ± 0 07*
RR (c/min)	28 1 ± 5 2	26 4 ± 5 7	10 3 ± 5 4	14 8 ± 5 5*
VT (L)	0 26 ± 0 06	0.21 ± 0 03^{+}	0 31 ± 0 13	0 29 ± 0 08
VE (L/min)	7 30 ± 2 10	5 30 ± 1.07^{+}	2 97 ± 1 60	3 98 ± 1 03*
VT/TI (L/s)	0 28 ± 0 08	0 22 ± 0 04^{+}	0 25 ± 0 10	0 24 ± 0 04
$P_{ET}CO2$ (mmHg)	48 0 ± 4 4	52 2 ± 6 6	62 5 ± 8 1	54 7 ± 6 6*

Conclusions: Opiates produce marked changes in breathing pattern. Their addition to halogenated agents affects mainly the processes that regulate timing through a delay in the inspiratory switch-off mechanism and to a greater extent through prolongation of expiratory time, while driving seems to hold steady due at least in part to increased $PETCO_2$

References

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A.239 Comparative effects of halothane and isoflurane on ventilation

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Background & Goal of Study: Halogenated anaesthetics have ventilatory depressant effects due to their effects on central control of breathing Each may have specific effects through actions either on timing or driving The present study aimed to compare the effects of halothane (HAL) and isoflurane (ISO) on breathing pattern, end-tidal CO_2 pressure ($PETCO_2$) and inspiratory occlusion pressure at 100 ms (P0 1)

Material & Methods: Seventy-four patients were enrolled in the study after institutional and individual consent forms were signed After anaesthetic induction and orotracheal intubation with thiopental and succynicholine Randomly the patients received 1 2 CAM of HAL (N = 37) or ISO (N = 37) in O_2 When patients breathed spontaneously, a continuous recording of ventilation and $PETCO_2$ were performed for 2 min Three manoeuvers of inspiratory occlusion were performed in order to P0 1 Inspiratory time (TI), TI to total time ratio (TI/Ttot), respiratory rate (RR), tidal volume (VT), minute ventilation (VE) and mean inspiratory flow rate (VT/TI) were calculated breath by breath P0 1 was averaged from the 3 manoeuvers Statistical analysis was performed with a *t* test

Results: The table shows the mean values (SD) for all parameters for each group

	HAL (N = 37)	ISO (N = 37)	*P*
TI (s)	0 96 (0 15)	1 02 (0 17)	NS
TI/Ttot	0 45 (0 03)	0 42 (0 04)	0 012
RR (c/min)	28 5 (4 8)	25 8 (5 8)	0 036
VT (L)	0 26 (0 05)	0 22 (0 04)	0 0001
VE (L/min)	7 28 (1 72)	5 54 (1 15)	0 0001
VT/TI (L/s)	0 28 (0 08)	0 23 (0 04)	0 0001
$PETCO_2$ (mmHg)	47 8 (4 6)	51 4 (6 7)	0 008
PO 1 (cmH_2O)	2 93 (0 98)	1.75 (0 78)	0 0001

Conclusions: ISO is more ventilatory depressant than HAL at the same MAC This difference is due to specific effects on timing because ISO produces a delay in the inspiratory switch on and on driving output because ISO reduces it Together, these effects produce a greater reduction in minute ventilation and hypoventilation

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A.240 Acute respiratory failure in patients after surgical thoracic oesophagectomy

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Background and Goal of Study: Respiratory complications are the main cause of morbidity after oesophagectomy. The mechanisms of lung injury following surgical oesophagectomy are unclear The aim of this study is to describe the onset of acute respiratory distress syndrome (ARDS) after transthoracic oesophagectomy in patients with oesophageal malignant tumors, and evaluate possible risk factors associated with this complication

Material & Methods: We have prospectively studied the respiratory complications in 28 patients who underwent surgical transthoracic oesophagectomy between January 1995 and June 1997 Several risk factors have been examined in order to evaluate its association with the development of ARDS A total of 60 parameters were analyzed in each patient 35 preoperative (including underlying disease, pulmonary function tests, nutritional state, risk index, etc), 10 variables referred to the surgical intervention and the tumor characteristics (surgical approach, tumor localization and characteristics, tumor stage, surgical duration, need of transfusion, etc), and 15 variables referred to the postoperative period (APACHE II score and TISS at admission in the ICU, pulmonary complications, reintubation, mechanical ventilation duration, SICU evolution, etc)

Results and Discussion: Fourteen patients (50%) presented some kind of pulmonary complication during the postoperative period 7 pneumonia or atelectasis, 2 tracheobronchitis, and 5 ARDS (18%) This latter group of patients with ARDS (mean age of 59.2 ± 10 7 years, APACHE II score of 18 6 ± 5 5, and TISS of 45.6 ± 5 5) had been extubated during the first 24 hours; however, on the third postoperative day developed hypoxemia and diffuse pulmonary infiltrates (Murray score >2.5) requiring reintubation and mechanical ventilation. Significant statistical differences ($p < 0\ 05$) between patients with and without ARDS were observed in preoperative FEV_1/FVC (62 ± 19 vs 75 ± 6), tumor location at the middle third of the oesophagus (100% vs 34%, p = 0 02) and mortality (60% vs 9%, p = 0 006)

Conclusions: ARDS is a frequent complication (18%) after surgical transthoracic treatment of oesophageal cancer, associated with high mortality (60%) A low preoperative FEV_1/FVC and location of the tumor at the middle third of the oesophagus have been found to be associated with

ARDS This latter factor may condition a longer lung manipulation during transthoracic oesophagectomy and en-block lymphadenectomy Postoperative conditions that allow a quick extubation on the postoperative period do not exclude the probability to develop ARDS.

A.241 Pulmonary gas exchange during hyperthermia

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Background: The efficacy and tolerance regarding pulmonary gas exchange of systemic Cancer Multistep Therapy (sCMT) by Ardenne was tested in patients with colorectal carcinoma This therapy consists of a whole body hyperthermia at a temperature of 42°C with additional chemotherapy, hyperoxaemia, and hyperglycaemia

Methods: During 11 sCMT treatments in six patients (aged from 37–54 years) during TIVA and inhalation of O_2-air mixture, pulmonary gas exchange and haemodynamics were examined at 4 time points: 1. at 37°C, before the warming-up, 2. in the warming-up phase at 40°C, 3 at 42°C; 4. in the cooling-phase at 39°C) The patients were ventilated in the volume controlled mode (PEEP 5–10 cmH_2O, respiratory rate 10–16/min, I E = 1.2, FiO_2 as to achieve a $paO_2 > 250$ mmHg) and metabolic monitoring was performed (Puritan-Bennett® 7200 AE and 7250) The haemodynamic monitoring consisted of a Swan-Ganz catheter (Baxter Explorer®), a lung water catheter positioned in the A femoralis (Pulsion COLD Z-021® and an arterial line (A. radialis). The patient was warmed with a water-filtered infrared-A irradiation (IRATHERM 2000®). Statistical test Wilcoxon rank sum test. Significance was defined by $p < 0.05$.

Results: The oxygen consumption increased significantly, as measured with indirect calorimetry using Fick's equation and measurement of the respiratory gas fraction. To achieve a normal $paCO_2$ (35–40 mmHg), minute ventilation (MV) was significantly increased with a maximum at 42°C (MV at 37°C: 7 4 l/min, at 42°C: 12.3 l/min [median], $p < 0.0001$) Concurrently oxygen delivery and cardiac output increased significantly ($p < 0.0032$ and $p < 0.001$, respectively). In contrast, arterial-venous oxygen difference remained constant. Alveolo-arterial oxygen partial pressure difference and intrapulmonary right-to-left shunt were significantly increased at 42°C ($p < 0.05$ and $p < 0.03$, respectively) and fell again during the cooling period, so that a comparison with the measurements at 37°C did not differ significantly The compliance of the lungs and the dead space remained unchanged Although the pulmonary vascular resistance fell moderately, mean pulmonary arterial pressure increased significantly parallel to the rise of CO Extravascular lung water remained within normal range (approx. 4 ml/kg).

Conclusions: Whole body hyperthermia during general anaesthesia and controlled respiration induced significant changes regarding pulmonary gas exchange. These changes were, however, moderate and were reversible during the cooling period Hence, for cardiac and pulmonary healthy patients no deterioration in pulmonary gas exchange has to be expected

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A.243 Pressure-controlled ventilation *vs* volume-controlled ventilation during general anaesthesia with peroperative respiratory system dynamic compliance changes

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Background and Goal of Study: In intensive care unit, PCV is widely used by physicians. This ventilatory alternative to VCV is claimed to improve alveolar ventilation and to decrease peak airway pressure during respiratory system compliance decreases, thereby limiting lung damage. Therefore we prospectively studied the respiratory mechanic parameters when comparing PCV to VCV during general anaesthesia with respiratory system dynamic compliance changes.

Patients and Method: After institutional approval, 23 ASA 1 or 2 patients scheduled for total hip replacement under general anaesthesia (thiopental, sufentanil, isoflurane in $50\%O_2/50\%N_2O$) were enrolled. Each patient was randomly assigned to receive successively PCV and VCV (Excel 7900, Ohmeda corp, USA) in dorsal decubitus position then in lateral decubitus position. Each patient was his own referee. The ventilatory targets: tidal volume (Vt) at 8 ml/kg, respiratory rate (RR) at 12 b/min, TI/Te ratio at 1/1.5 and end expiratory pressure at 0 cm H2O were identical between both ventilatory modes and both positions. After 10 minutes of ventilatory stability in each mode and each position, other ventilatory parameters were measured (Capnomac Ultima, Datex corp, Finland) at the proximal port of the tracheal tube: peak airway pressure (P peak, cmH2o), airway pressure level at end-inspiration (Pplat, cmH2O), total respiratory system compliance (Crs, ml/cmH2O), minute ventilation (VE, L/min) Pet Co2 (cmH2O), Spo2, mean arterial pressure (map) and heart rate (hr) were also continuously monitored Mann and Withney tests were used.

Results: Vt, RR, Ti/Te, SpO2, map and hr values were similar in both ventilatory modes and positions. Other peroperative respiratory variables are reported in the table

	VCV		PCV	
	dorsal dec	lateral dec	dorsal dec	lateral dec
Crs	51 0 ± 11 2	40 0 ± 8 9°	51 9 ± 10 7	41 7 ± 8 4°
Ppeak	15 1 ± 3 3	17 ± 3 5°	13 4 ± 2 7*	14.7 ± 2 5*°
Pplat	14 3 ± 3 0	16 0 ± 2 9°	13 3 ± 2 *	14 6 ± 2 5*°
VE	5 5 ± 1 1	5 5 ± 1 0	5 5 ± 1 0	5 5 ± 1 0
PetCo2	32 2 ± 1 9	32 2 ± 2 3	32 1 ± 2 1	32 ± 52 6

*p < 0 05 versus VCV, °p < 0 05 versus dorsal decubitus

Discussion and Conclusion: During general anaesthesia with peroperative respiratory system compliance decreases, PCV allows a constant targeted Vt with lesser Ppeak and Pplat than VCV. These results may be due to the decelerated inspiratory flow and the improved alveolar gaz distribution. Further studies are necessary to define the advantages of PCV in routine anesthetic procedures and in patients dependant of hemodynamic and respiratory stability.

A.244 Pressure-controlled ventilation with a laryngeal mask airway during general anaesthesia

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Background and Goal of Study: When using a LMA with positive pressure ventilation, air leaks are directly proportional to the airway pressure (1). In an other hand, PCV is usually used with tracheal tubes without inflatable cuff in children to improve the targeted tidal volume (Vt), thereby limiting gastric insufflation or neck leaks Therefore we prospectively studied the respiratory mechanic parameters and air leaks when comparing PVC to volume controlled ventilation (VCV) during general anaesthesia using a LMA.

Patients and Methods: After institutional approval, 28 ASA 1 patients scheduled for minor orthopedic surgery procedures under general anaesthesia (propofol, fentanyl, 50% O2 50% N2O) were enrolled Each patient was randomly assigned to receive successively PCV and VCV (Excel 7900, Ohmeda corp, USA) with the LMA, in dorsal decubitus position. Each patient was his own referee. The ventilatory targets: inspiratory tidal volume (Vti) at 8 ml/kg, a respiratory rate (RR) at 12 b/min, a Ti/Te ratio at 1/1.5 and an end expiratory pressure at 0 cm H2O were identical between both ventilatory modes. After 10 minutes of ventilatory stability in each mode, respiratory parameters were measured (Capnomac Ultima, Datex corp, Finland) at the proximal port of the tracheal tube: total respiratory system compliance (Crs), expiratory tidal volume (Vte), air leaks around the LMA, minute ventilation (VE), peak airway pressure (Ppeak). PetCO2, SpO2, mean arterial pressure and cardiac frequency were continuously monitored. Mann and Withney tests were used for statistical comparisons.

Results: Vti, RR, Ti/Te, SpO2 and hemodynamic variables values were similar in both ventilatory modes. Other peroperative respiratory variables are reported in the table

	Crs ml/cmH2O	Ppeak cm/H2O	Vte ml	Leaks ml	VE l/min	PetCO2 cm/H2O
VCV	54 ± 9	15 ± 5	508 ± 78	60 ± 36	6 ± 1	32 ± 3
PCV	54 ± 10	12 ± 3*	529 ± 14*	38 ± 20*	6.4 ± 1*	33 ± 3

*p < 0 05 versus VCV

Discussion and Conclusion: In comparison to VCV, PCV during general anaesthesia produces lower peack airway pressure for the same targeted Vti and as such decreases the leaks around the LMA thereby improving Vte and VE values. Additional studies are necessary to define the benefits of PPV in routine anesthetic procedures.

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A.245 Influence of tracheal stenosis on high frequency jet ventilation: a model study

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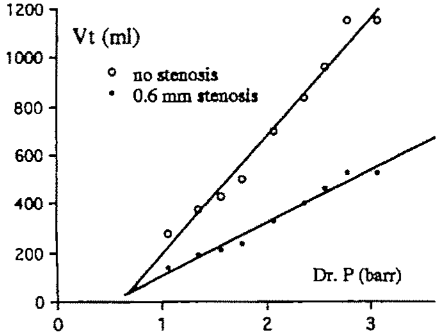
Aim of the Study: High Frequency Jet Ventilation (HFJV) is commonly used during endoscopic laser resection of tracheal stenosis (1). We measured lung volumes and airway pressures at variable HFJV settings using a lung model with tracheal stenosis of different diameters.

Material and Methods: A lung model (Demonstration Lung LS 800 Dragerwerk) was ventilated using HFJV (MK 800, Acutronic Medical System, Switzerland) through a triple-lumen tracheal tube (Hi-Lo) at increasing driving pressure (Dr P), frequency (f) and I/E ratio. 2 cm thick diaphragms were inserted distally to the tracheal tube to simulate stenoses of 9, 8, 7 and 6 mm of diameter. Magnetometer coils were attached on each end of the bellows to assess Tidal Volume (Vt) and Increase in Functional Residual Capacity (FRC). Airway pressures were measured with a pressure transducer below the tracheal stenosis.

Results and Discussion:

Results and discussion:



Without stenosis, Vt varied linearly with increases in Dr P or I/E. Vt decreased when f increased. High Dr P, frequency or I/E settings resulted in PEEP and pulmonary hyperinflation

Narrowing the tracheal stenosis to 6 mm decreased Vt at any HFJV setting ($p < 0.05$), but had no significant effect on PEEP or FRC.

Conclusion: Our study suggests that, during HFJV, tracheal stenoses mainly produce hypoventilation when the injector is proximal to the tracheal narrowing Adjusting the ventilator to an adequate Vt might increase the risk of pulmonary hyperinflation

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A.246 High-frequency ventilation techniques improve oxygenation in patients with impaired pulmonary function

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Background and Goal of Study: High-frequency (HF) ventilation techniques have been introduced as alternative ventilatory modalities during laryngeal and pulmonary surgery, in patients with bronchopleural fistulae, or to improve impaired oxygenation (1) To study the proposed beneficial effects of HF ventilation on oxygenation we treated ICU patients with either HF oscillatory ventilation (HFO) or HF jet-ventilation (HFJV)

Materials and Methods: 36 patients of a surgical intensive care unit (25 male/11 female, 51 ± 18 yrs) were ventilated with a pneumatic HFO ventilator (VDR4, Percussionaire Corp., Idaho, U.S A) or an electronic prototype superimposed-HFJV respirator (Alexander I, Fa. Reiner, Austria) Superimposed HFJV was characterized by simultaneous application of low-frequency and high-frequency jet-streams for adequate CO_2 elimination through small-bore cannulas of a special jet-adapter connected to the conventional endotracheal tube. Indications for HF ventilation were pulmonary insufficiency (20), atelectases (13), and bronchopleural fistula (3) HF rates of HFJV and HFO were set between 500 and 700/min, the conventional respiratory rates ranged from 10–18/min. Oxygenation index (OI, paO_2/FiO_2) and PIF (PEEP × I:E × FiO_2) were evaluated before and after 24 hours of continuous HF ventilation. Data (mean ± SD) were statistically analyzed using the paired *t*-test ($p < 0.01$).

Results: HFV resulted in improved oxygenation in 27 of 36 patients (75%). OI increased in 21 responders to HFJV from 131 ± 71 to 181 ± 87, PIF could be reduced in 12 of these patients Likewise, OI increased in 7 responders to HFO (88%) from 121 ± 37 to 196 ± 84, PIF could be reduced in 6 of these patients CO_2 levels (50 ± 20 *vs* 49 ± 16 mmHg) did not increase during 24 h of HFV No ventilator associated complications were observed

Conclusion: Although the mechanisms of HFV have not been clarified in the past, superimposed HFJV and HFO are safe and effective to improve impaired oxygenation. These HFV techniques also facilitate adequate ventilation avoiding an increase in arterial CO_2 levels. However, not all patients may respond to HFV and will need additional therapeutic interventions to improve pulmonary function.

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A.247 Alveolar pressure measurement in patients with acute lung injury (ALI)

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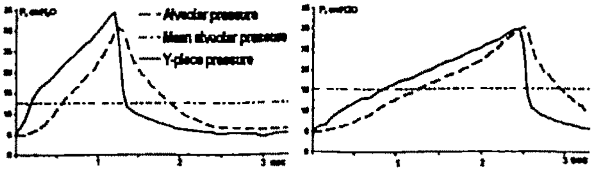
Background and Goal of Study: To avoid barotrauma it is important to monitor alveolar pressure So far alveolar pressure has been estimated from pressure measured proximal to the endotracheal tube. This pressure is distorted by tube resistance We have developed a method for continuous measurement of alveolar and y-piece pressure together with ventilatory volumes and flows from a side stream spirometer using a Datex AS/3 monitor

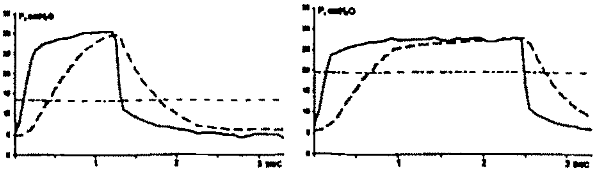
Materials and Methods: In seven ALI patients, a thin pressure line was introduced through an airtight cuff at the y-piece and placed in the trachea Tracheal pressure was plotted versus tidal volume Assuming equal inspiratory and expiratory resistances the level of the alveolar pressure was determined from the ratio of inspiratory and expiratory flow at the same ventilation volume Alveolar and y-piece airway pressures were plotted versus time

Results & Discussion: During pressure control ventilation and respiratory freq 16, the time delay before alveolar pressure reached a plateau was app. 1 sec and independent of I:E ratio. During volume control ventilation the delay was very short but pressure rises slowly, continuously throughout inspiration. Mean alveolar pressure increases stepwise when I:E ratio was prolonged from 1:2 to 2:1 during pressure control despite no intrinsic PEEP occurring. During volume controlled ventilation mean alveolar pressure was low at I:E ratio 1:2 and increased slightly at I:E ratio 2:1. Overall mean alveolar pressure was 25–30% lower during I:E ratio 1:1 and 2:1 with volume compared to pressure control ventilation

Volume controlled ventilation



Pressure controlled ventilation



I:E ratio1:2 **I:E ratio 2:1**

Conclusions: Pressure control inverse I:E ratio ventilation produce higher mean alveolar pressure as alveolar plateau pressure level is reached faster than during volume control despite the same tidal volume, peak alveolar and end expiratory alveolar pressure The y-piece pressure overestimates inspiratory pressure and underestimates expiratory pressure profile. Mean y-piece pressure was however close to the mean alveolar pressure irrespective of ventilatory mode

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A.248 Comparison of expiratory washout and optimized conventional mechanical ventilation during permissive hypercapnia

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Background and Goal of the Study: EWO can be used as an adjunct to mechanical ventilation to reduce $PaCO_2$. Optimizing conventional ventilation by increasing respiratory rate to the limit of auto-PEEP and reducing the instrumental dead space (by removing the connecting tube between the endotracheal tube and the Y piece) could be an attractive alternative The aim of this study was to compare EWO, OCMV and the combination of both modes (OCMV + EWO) during permissive hypercapnia (PH) in patients with ARDS.

Patients and Methods: After local ethic committee approval and informed consent, 6 sedated and paralyzed patients (mean age = 45 ± 15 yrs) with severe ARDS (LISS = 3.2 ± 0.5 and PaO_2/FIO_2 at admission = 137 ± 50 mmHg) were studied $PaCO_2$ and pH values were 84 ± 24 mmHg and 7.21 ± 0.12 respectively during PH with the following ventilatory settings respiratory rate 18 b/mn; tidal volume adjusted in order to obtain an inspiratory plateau pressure (Pplat) equal to the upper distending pressure minus 2 cmH_2O; PEP equal to the lower inflection point plus 2 cmH_2O. The 3 conditions were performed in a random order and preceded by a return to the control condition (PH). Pplat was kept constant by adjustment of the external PEEP in all conditions. Values are presented as mean ± SD.

Results: The changes in $PaCO_2$ and pH induced by OCMV and EWO were similar (−24 ± 10 vs −23 ± 10 mmHg and +0 15 ± 0 01 vs +0.15 ± 0.01, NS). Both techniques had additive effects and their combination induced a reduction in $PaCO_2$ of −40 ± 17 mmHg and an increase in pH of +0.26 ± 0.06. In order to maintain Pplat constant, external PEEP had to be reduced by 5.3 ± 2 1 cmH_2O during EWO and by 7.3 ± 1.3 cmH_2O during the combination of OCMV ± EWO No change in external PEEP was necessary during OCMV alone. PaO_2 and cardiac output remained constant in all the conditions tested.

Conclusion: The conventional ventilation optimized by increasing respiratory rate and reducing the instrumental dead space is as efficient as expiratory washout for CO_2 removal in patients with ARDS and permissive hypercapnia The combination of both techniques have additive effects.

A.249 Effectiveness of total and partial expiratory washout in permissive hypercapnia

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Background and Goal of the Study: The efficacy of EWO delivered during the entire expiratory phase has been recently demonstrated[1] However, one of the drawback of the technique is to generate intrinsic PEEP and to increase inspiratory plateau airway pressure, thereby increasing the risk of barotrauma. We hypothesized that delivering EWO only during the late phase of the expiration might reduce this side effect

Patients and Methods: After local ethic committee approval and informed consent, 7 sedated and paralyzed patients (mean age = 45 ± 17 yrs) with severe ARDS (LISS = 3 2 ± 0 5, PaO_2/FIO_2 at admission = 126 ± 55 mm Hg) were studied $PaCO_2$ and pH values were 97 ± 35 mmHg and 7 16 ± 0 12 respectively with the following ventilatory settings· respiratory rate 18 b/mn; tidal volume adjusted in order to obtain a plateau pressure equal to the upper distention point minus 2 cmH_2O; PEEP equal to the lower inflection point plus 2 cmH_2O EWO was limited to the last second of the expiratory phase in partial EWO and delivered during the entire expiration in total EWO Total and partial EWO were studied in cross over, each preceded by a return to the control condition. Plateau pressure was kept constant by adjusting external PEEP in all conditions tested. Values are presented as mean ± SD

Results: Total and partial EWO induced similar decreases in $PaCO_2$ [−31 ± 24 mmHg (−29%) vs −33 ± 21 mmHg (−34%)] and increases in pH [+0.16 ± 0 01 vs +0 18 ± 0.01; NS]. As compared to the control condition, PaO_2 was significantly lower during partial EWO [−50 ± 50 mmHg (−26%)]. To maintain inspiratory plateau pressure constant, external PEEP had to be reduced similarly in both modes [−5.7 ± 2 1 (46%) vs −5.7 ± 1.6 cmH_2O (47%)]. However the minimal airway pressure was lower during partial EWO than during total EWO [−51% vs −33%, $p < 0.01$].

Conclusion: The implementation of EWO during the late phase of the expiration showed no benefit in terms of CO_2 removal and intrinsic PEEP reduction. It may even be detrimental on PaO_2 because of alveolar derecruitement occurring during the early phase of the expiration.

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A.250 Effect of pipecuronium in isolated human bronchi

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Introduction: Airway caliber is determined by the balance of pre- and postjunctional muscarinic receptor activity. Stimulation of postjunctional muscarinic receptors induces bronchoconstriction By contrast stimulation of prejunctional muscarinic receptors inhibits acetylcholine (Ach) release, reducing airway smooth muscle contraction Neuromuscular blockers can interact with pre-and postjunctional muscarinic receptors (1) The current experiments examined the effects of pipecuronium on pre- and postjunctional muscarinic receptors in isolated human bronchi

Methods: Isolated human bronchial rings (3-mm ID) were suspended in organ baths filled with physiological salt solution (PSS) at 37°C and aerated with 95% O_2 and 5% CO_2 They were stretched until the contractile response to electric field stimulation (EFS) was maximal and constant (optimal length); they were kept at this length throughout the study Four bronchial rings from each of six patients were first incubated with 10^{-6} M Tetrodotoxin (TTX) and then contracted with Ach (cumulative half-log increments, 10^{-9} to 10^{-2} M). Thereafter they were washed with PSS containing TTX, incubated with pipecuronium 10^{-7} M (n = 6), 10^{-6} M (n = 6), 10^{-5} M (n = 6) and again contracted with Ach. Four bronchial rings from each of the same six patients were incubated with either 10^{-7} M, 10^{-6}M or 10^{-5} M pipecuronium; pilocarpine (10^{-9} to 10^{-4} M) was then added The fourth ring from each patient served as a control All four rings were contracted every 3 minutes for 30 sec. by EFS (25 Hz, 25 v, 0.5 ms), before and after the addition of each concentration of pilocarpine

Results: Pipecuronium (10^{-7}, 10^{-6}, 10^{-5}M) did not alter the contractile responses to Ach, suggesting no inhibitory postjunctional M_3-receptor effect. By contrast, pipecuronium (10^{-6} to 10^{-5} M) shifted the concentration-response curve of pilocarpine significantly ($P < 0.05$) to the right, suggesting an inhibitory effect on prejunctional M_2-receptors. Pipecuronium 10^{-5} M but not 10^{-6} M and 10^{-7} M reduced significantly the resting force, but the right shift of the pilocarpine-concentration-response curve was independent of the increase in the resting force

Conclusions: In isolated human bronchial rings pipecuronium is a M_2- but not M_3- muscarinic receptor antagonist. Pipecuronium could therefore increase reflex-induced bronchoconstriction

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A.251 Comparative effects of nitric oxide, enflurane and isoflurane on respiratory resistance with methacholine-induced bronchoconstriction

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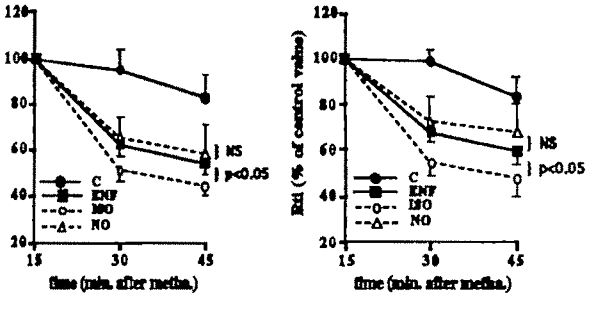
Background and Goal of Study: The aim of this study was to compare the effects of NO, enflurane and isoflurane on respiratory resistance using flow-interruption technique[1].

Materials and Methods: Twenty eight cats were divided into 4 groups according to the agents administered, C (control), NO (20 ppm of NO), ENF (1 MAC of enflurane) and ISO (1 MAC of isoflurane) groups. Tracheal pressure was measured at 2–3 cm beyond the distal end of the tube After measuring the baseline value, methacholine (25 μg/kg/min) was infused to induce bronchoconstriction which was continued throughout the experiment Agents were administered for each group 15 min after methacholine infusion (control value) via low pressure inlet of the ventilator Measurements were made every 15 min. IMV was applied with Servo 900C® ventilator. Inspiratory flow rate and tidal volume were fixed throughout the experiment for each subject Pressure, volume and flow were monitored with Bicore CP100® pulmonary monitor The data were transferred to a PC and analyzed by a processing software. Total respiratory (Rrs), airway (Raw) and tissue (Rti) resistances were calculated[1]. One way ANOVA with Student-Newman-Keuls *post hoc* test was used for statistical analysis.

Results and Discussion: The figures show the changes of Raw and Rti.



Conclusion: For NO, ENF and ISO, both Raw and Rti were reduced ISO was more potent than ENF in contrary to the previous report[2]. NO was as effective as ENF in reversing bronchoconstriction.

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A.252 Inhaled nitric oxide improves ventilation/perfusion relationship after anoxic ischaemia and reperfusion in isolated rabbit lungs

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Background and Goal of Study: Ischaemia and reperfusion cause damage to the lung. The tissue injury is associated with pulmonary hypertension and impaired endothelial permeability. It is assumed that a decreased production or neutralization of endogenous nitric oxide (NO) contributes to the lung injury. Inhalation of NO has been shown to attenuate the reperfusion injury. This study was designed to examine the influence of exogenous

NO on ventilation/perfusion-relationship (V_A/Q) after anoxic ischaemia and reperfusion in isolated, buffer perfused rabbit lungs

Material and Methods: Two hours of anoxic ischaemia (95% N_2, 5% CO_2) were followed by 90 minutes of normoxic reperfusion (21% O_2, 5% CO_2) (n = 9) NO was administered at the start of reperfusion (n = 4) Pulmonary artery pressure (PAP), double occlusion pressure, and left atrial pressure as well as lung weight were measured V_A/Q-relationship was determined before anoxic ischaemia and after 15, 30, 60, and 90 minutes of reperfusion using the multiple inert gas elimination technique (MIGET) Inhaled NO was measured by chemiluminescence

Results: Anoxic ischaemia and reperfusion resulted in a severe V_A/Q mismatch The lung weight gain limited the reperfusion period to 30 min Shunt flow increased almost 10 fold. The log dispersions of perfusion and ventilation were broadened The log mean of perfusion was shifted to the left whereas the log mean of ventilation showed a movement towards high V_A/Q-areas Inhalation of NO attenuated lung weight gain and PAP, and prolonged the reperfusion period to 90 min The V_A/Q-relationship was improved. Shunt flow was reduced The V_A/Q-relationships of ventilation and perfusion showed a unimodal and narrow log dispersion and a matched log mean within normal limits.

Table V_A/Q-ratio of perfusion after anoxic ischaemia

	NO [ppm]	Pre ischaemia	Time [min]		
			135′	150′	210′
Shunt	0	1 8 ± 0 5	17 2 ± 6 3#	31 5 ± 7 2#	
	10	2 1 ± 0 4	3 5 ± 0 9	4 9 ± 0 6	6 0 ± 2 2
[%]	control	2 0 ± 0 5	2 1 ± 0 2	1 7 ± 0 5	2 2 ± 0 4
Low	0	0 0 ± 0 0	19 3 ± 7 1#	7 8 ± 2 8	
V/Q	10	0 5 ± 0 4	2 6 ± 1 7	2 8 ± 1 4	2 0 ± 1 4
[%]	control	0 0 ± 0 0	0 0 ± 0 0	0 0 ± 0 0	0 0 ± 0.0
Normal	0	98 4 ± 0 5	62 7 ± 7 5#	59 7 ± 6 8#	
V/Q	10	97 4 ± 0 2	94.0 ± 1 7	92 5 ± 1 9	92 0 ± 3 4
[%]	control	98 0 ± 0 5	97 9 ± 0 2	98 3 ± 0 5	97 8 ± 0 4

Values are means ± SEM, # = $p < 0\ 05$ vs control and 10 ppm NO

Conclusion: Inhaled nitric oxide is a useful agent to reduce reperfusion injury and to prevent the V_A/Q-mismatch after a prolonged period of anoxic ischaemia

A.253 Effects of inhaled nitric oxide, L-NAME and the association of both in an experimental model of one-lung ventilation

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Background and Goal of Study: During one lung ventilation (OLV) inhaled nitric oxide (NO) increases pulmonary blood flow to the ventilated lung and improves gas exchange, although this effect does not seem to be dose- dependent (1) Intravenous N^G-Nitro-L-Arginine (L-NAME), a nitric oxide synthase inhibitor, by increasing hypoxic pulmonary vasoconstriction (HPV) reduces right to left shunt in experimental models (2) We compared the effects of inhaled NO, i v. L-NAME, and the association of both upon partial arterial oxygen pressure (PaO_2) and pulmonary blood flow in an experimental model of OLV.

Material and Methods: Seven anaesthetized sheep were studied under left lung ventilation. Left pulmonary blood flow (LPBF) was measured by an electromagnetic probe attached to the left pulmonary artery Measurements of systemic and pulmonary haemodynamics, and LPBF were performed at baseline conditions, after 10 minutes of NO inhalation (40 ppm), after a second basaline period without NO, 30 minutes after 30 mg.Kg^{-1} of i v. L-NAME and after inhalation of NO (40 ppm) for 10 minutes Arterial and mixed venous blood gas tensions were also measured

Results and Discussion: Percentages of increase of PaO_2 and LPBF with each treatment are shown in table 1. NO alone produced a significant increase in PaO_2 and in LPBF Intravenous L-NAME alone increased blood flow to the ventilated lung, without significant effect on PaO_2 The association of both treatments resulted in a dramatic and significant increase in PaO_2 and LPBF compared to basaline period and to NO inhalation alone

Table 1 Increase in PaO_2 and LPBF

	NO	L-NAME	L-NAME + NO
PaO_2 (%)	13 4 (1 9)*	10 1 (6 8)	76 7 (12 1)*a
LPBF (%)	10 9 (3 2)*	38 7 (10 7)*	78 6 (13 1)*a

Mean (SE), *$P < 0\ 05$ versus basal values, a$P < 0\ 05$ versus NO values (t-test)

Conclusions: The association of L-NAME and NO has a synergistic effect upon gas exchange and redistribution of pulmonary blood flow in this model of OLV

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A.254 Role of endogenous nitric oxide in the adaptation of the pulmonary arterial bed to one-lung ventilation during thoracic surgery

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Background and Goal of Study: NO is now stablished as a biological mediator of clinical relevance (1) Its role as mediator in the pulmonary vascular changes following acute hypoxia is not well stablished (2) The aim of this study is to evaluate the changes in the endogenous NO concentrations during one lung ventilation (OLV) and its effects on the pulmonary haemodynamics.

Materials and Methods: A prospective study was carried out on 20 patients (experimental group) during pulmonary resection under OLV, and 10 cases (controls) during mediastinoscopy using conventional ventilation In the experimental cases, a Swan-Ganz catheter was inserted To evaluate the endogenous NO production, measured as concentration of nitrite ions by a cuantitative colorimetric assay (Griess reaction), in the experimental group a blood sample was obtained from superior cava vein after anaesthesia induction and 10 minutes after the onset of OLV, in control group, the blood samples were obtained at equivalent period. At the same periods of time, hemodynamic parameters were measured in the experimental group, pulmonary artery pressure (PAP), cardiac index (CI), pulmonary vascular resistance (PVR) were registered In both groups, mean values of each variable were compared using a paired-T-test and analysis of variance.

Results and Discussion: In the experimental group, nitrite concentration increased significantly from 7 1 μM to 12 7 μM after OLV ($p = 0\ 02$). In the control group, no differences were found at the same times (8.7 and 8 1 μM respectively). The PAP did not change significantly after OLV (19 and 18 4 mmHg) PVR showed a significant decrease after OLV (163 46 and 134.2 din seg/cm –5, respectively, $p = 0.002$). The CI increased significantly from 2.9 to 3 5 (L/min/m2) after OLV ($p < 0.05$)

Conclusion: This study shows an increase of endogenous NO during OLV and a decrease in pulmonary vascular resistance without modification in PAP. These results may be compatible with a role of endogenous pulmonary production of NO in the adaptative vascular pulmonary changes following to an acute hypoxic phenomenon

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A.255 Effects of thoracoscopy on the immediate postoperative pulmonary function

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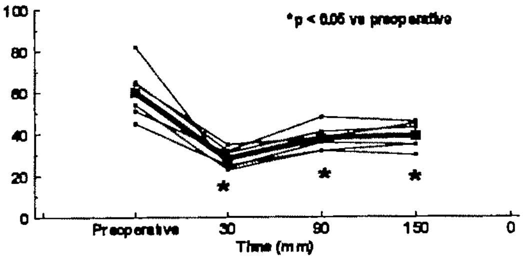
Background & Goal of the Study: Thoracoscopy (VATS) became the procedure of choice for many intrathoracic procedures. There are several differences between VATS and standard thoracotomy less postoperative pain and better early pulmonary function. The decrease of FEV1 after VATS is about half that expected after thoracotomy (1) The aim of this study was to evaluate the pulmonary function (PF) in the early postoperative period in patients undergoing lung biopsies by VATS

Materials and Methods: After IRB approval and informed consent, the PF of six male patients (age 50 3 ± 10 6) were studied with a hand-held spirometer (Respiradyne II, Sherwood Med, Watertown, NY) preoperatively and at 30, 90, and 150 min after extubation in the recovery room VATS was performed under general anesthesia with double-lumen endotracheal tube intubation Anesthesia was with intravenous propofol supplemented with sufentanyl and atracurium as muscle relaxants All patients were extubated in the operating room at the end of the procedure All the procedures were performed by the same surgeon Postoperative pain was controlled by 0 5% bupivacaine intercostal blocks in all patients In the recovery room, patients received 40% 02 supplementation Wilcoxon rank sum test was used for analysis FEV1 and FVC are expressed as % of predictive value Values are expressed as median and CI 95%, $p < 0\ 05$ was significant.



Results: The hemodynamic parameters (blood pressure, heart rate), PaO2, PaCO2 and SaO2 were stable during the procedure, and did not change significantly during the postoperative period. The individual FEV1 values are represented in Fig 1. VATS biopsy impaired the PF maximally at 30 min in the postoperative period, when FEV1 and FVC decreased to 52.5% and 53.6% of the preoperative values, respectively. At 150 min after the procedure FEV1 and FVC were improved, but they still remained at 66% and 62% of the preoperative values, respectively.

Conclusion: In contrary to the general belief, there is a significant decrease of FEV1 and FVC in the immediate postoperative period after VATS, even without resection of lung tissue. The degree of impairment is similar as can be seen after lobectomy performed by thoracotomy (2).

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A.256 Abdominal wall retractor technique vs pneumoperitoneum laparoscopic surgery. Implications for anaesthetics

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Objective: The goal of our study is to compare the anesthetics implications of two different techniques for laparoscopy cholecystectomy (LC). classic pneumoperitoneum and abdominal wall retractor technique.

Material and Methods: Two homogeneous groups of patients scheduled for LC. The exclusion criteria were: morbid obesity, severe cardiorespiratory disease and previous abdominal surgery. Group I (n = 20): pneumop. Group II (n = 20). a.w retractor (Ongin®). The same anesthetic technique was used in both groups. Haemodynamics monitoring included the standard, plus non invasive CO through an oesophageal doppler probe (ODM II®). Ventilatory parameters monitored by Capnomac Ultima Datex® Data was collected at prefixed times: T0: 5 min post induction (basal), T1: 5 min post the peumop. or a w retractor was placed (in anti-Tren position). T2: 30 min. later. T3: 5 min post the retractor or pneumop. was removed

Results: Table 1 shows results There are no significative differences between both groups in terms of haemodynamic parameters a discrete ↓ CO and a 20% ↑ of SAP, DAP from basal values was noted at T2. There are statistical significant differences in terms of ventilatory measures in Group I (increase of PIP, PP, Raw and ET-C02 and a decrease in compliance)

Table Changes of ventilation and haemodynamics

	(T0)	(T1)	(T2)	(T3)
CO (N)	5 2 ± 1.4	4.4 ± 1.9	5 2 ± 1 5	5 7 ± 1.7
CO (R)	4 9 ± 1.3	4 5 ± 1 3	5 5 ± 1 8	5 2 ± 1 9
PIP (N)	21 8 ± 5 5	26 3 ± 6 5	26 3 ± 4 7	21 4 ± 3 5
PIP (R)	18 3 ± 2 4	16 8 ± 2 1	17 ± 2	16 8 ± 1.6
PP (N)	16 1 ± 4 8	19 9 ± 6.1	20 9 ± 3 4	16 1 ± 3 5
PP (R)	12 3 ± 2.1	11 8 ± 1.5	11 6 ± 1 7	11 2 ± 1 3
C (N)	45 3 ± 8 8	32 3 ± 7 3	31 6 ± 4 3	43 8 ± 7 9
C (R)	58 1 ± 18	60 2 ± 14 5	59 2 ± 14.6	56 8 ± 12 6
Tiff (N)	84.9 ± 6 5	85 2 ± 6.6	88 2 ± 4	83 9 ± 5 1
Tiff (R)	84 7 ± 6 8	82 5 ± 6 4	84 8 ± 7 5	87.2 ± 6 9

Variables (mean ± SD) N Pneumoperitoneum, R Retractor, CO. Cardiac Output (l/min), PIP. Peak Inspiratory Pressure, PP Plat Pressure (cm H_2O), C Compliance (ml/cm H_2O)

Conclusion: Physiopathological changes induced by lap. surg are well tolerated in healthy patients Nevertheless, in patients with severe cardiorespiratory conditions, the pneumop can produce significant alterations in cardiac and pulmonary functions and the use of pneumoperitoneum should be avoided In those cases the a.w retractor should be the choice due to its minimal physiological changes.

A.257 Oxygen homeostasis during laparoscopic procedures in morbidly obese patients

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Background and Aim: The cardiopulmonary consequences of the CO2 pneumoperitoneum seem well tolerated in the morbidly obese patients[1, 2] The higher metabolic demand of the MOP results in increased oxygen consumption (VO2). The aim of this study was to analyse the oxygen transport and venous admixture in the MOP during laparoscopic procedure.

Methods: General anaesthesia (sufentanil, N2O 50%, isoflurane) was administered in 13 informed patients (BMI > 40) scheduled for laparoscopic gastroplasty Arterial, venous and mixed venous oxygen content were measured from samples collected into the arterial, central venous line and distal hole of a pulmonary arterial catheter at different times during the procedure. The usual hemodynamic parameters including cardiac output were recorded at the same times. Data were analysed by analysis of variance (MANOVA); the univariate F-Test was used with each patient being his own control. We considered a statistical significance for a $p <$ 0 05

Results and Discussion: CO2 insufflation with an intra abdominal pressure of 17 mmHg did not modify the arterial and venous oxygen content The VO2, SVO2 and DO2 remained in the same range throughout the procedure. Following the release of pneumoperitoneum, DO2 increased (80%, p < 0.01) in combination with an increase in VO2 (88%, p = 0.01) and a slight increase in SVO2 (5%, p = 0.06) This study shows that MOP experienced few changes in oxygen homeostasis during laparoscopy despite an increased metabolic demand and a preoperative disposition to hypoxemia. VO2, DO2 and SVO2 increases were related to the 100% oxygen delivery at the end of anaesthesia.

Discussion: This study confirms that pneumoperitoneum is well tolerated in MOP

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A.258 Effect of pneumoperitoneum on Va/Q in laparoscopic cholecystectomy patients

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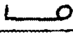
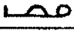
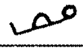
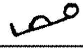
Background and Goal of Study: It has been shown that pneumoperitoneum (PP) reduces venous admixture (as assessed by indirect calculation of the shunt formula) and increases arterial oxygen tension (PaO_2) in cardiopulmonary healthy subjects (1). In the present study, the ventilation-perfusion (V_A/Q) relationships were evaluated by the multiple inert gas elimination technique (2), before and during PP to obtain a direct measure of the pulmonary shunt.

Materials and Methods: After informed consent and approval of the local ethics committee, nine cardiopulmonary healthy patients (ASA I), scheduled for laparoscopic cholecystectomy, (3 males, 6 females) with a mean age of 42 years were included. After premedication and anaesthesia, the patients had a radial arterial line and a thermodilution catheter percutaneously introduced into the pulmonary artery guided by pressure tracing. Six inert gases dissolved in physiologic saline solution were infused at a constant rate into a peripheral vein. After a stabilization period, samples of arterial and mixed venous blood and mixed expired gas were collected The concentrations of the inert gases in the blood and expired gas samples were analyzed by gas chromatography and the retention and excretion of each gas were calculated. The data were processed to get representative distributions of V_A/Q. Measurements were made in the supine position before and after establishment of PP by insufflation of carbon dioxide to an intraabdominal pressure level of 11–13 mmHg. After PP induction, measurements were made in the head-up tilt position and repeated after 30 minutes. Statistical analysis was performed using ANOVA Data are presented as means ± SD, p < 0.05 was considered significant.

Results and Discussion: Induction of PP significantly decreases the pulmonary shunt (p < 0.05) and increases PaO_2, in analogy with a previous study (1). During surgery, the shunt is elevated towards the pre-PP level. The cause of the present changes is unclear. It is suggested that the increased airway pressure may act as an intrinsic PEEP, counteracting atelectasis formation and shunt. Also, a transmission of the increased intraabdominal pressure to the thorax may change local perfusion pressures in favour of an optimized ventilation-perfusion matching, although the diaphragm is shifted cranially by PP.

Position				 30 min
Paw (cmH_2O)	16 ± 4.7	24 ± 4 5*	22 ± 3 6*	22 ± 4 3*
CO (L/min)	4 2 ± 0 7	4 7 ± 1 0	4 0 ± 0 9	4 1 ± 1 1
Shunt (%)	5 8 ± 4 5	4 1 ± 3.2*	3 2 ± 2 8*	5 2 ± 3.4†
PaO_2 (kPa)	21.7 ± 5 8	24 7 ± 4 8*	24 2 ± 4 2*	23 0 ± 4 6
MPAP (mmHg)	13 ± 2	18 ± 2*	9 ± 1*†	13 ± 3†

* denotes significant difference from before PP, p < 0 05, † denotes significant difference from previous measurement

Conclusion(s): In healthy subjects, PP at an intraabdominal pressure level of 11–13 mmHg causes transient reduction of the pulmonary shunt

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A.259 Estimating pulmonary shunt fraction in hypercapnic patients using a physiology simulator

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Background and Goal of Study: Calculation of pulmonary shunt fraction (Qs.Qt) in patients on the Intensive Therapy Unit (ITU) allows prediction of oxygen requirements and provides a means of assessing disease progression and the effect of interventions [1]. However, pulmonary artery catheterisation is required for its calculation, exposing patients to additional risks The iso-shunt diagram may be used to estimate Qs.Qt from the arterial oxygen tension (PaO_2) and the inspired oxygen fraction (F_IO_2) but is inaccurate during hypercapnia ($PaCO_2$ > 5.3 kPa) because of complex oxyhaemoglobin dissociation and alveolar gas effects. In this study we assessed the ability of a physiological simulator to estimate Qs:Qt in hypercapnic patients receiving intensive therapy.

Materials and Methods: The Nottingham Physiology Simulator (NPS) is a validated computer simulation of original, comprehensive physiological models. Iso-shunt lines have been constructed using the simulator and their agreement with Nunn's iso-shunt diagram is close and consistent Qs.Qt was measured in 20 randomly selected, hypercapnic patients on the ITU in whom a pulmonary artery catheter was present Qs·Qt was subsequently estimated in each subject by entering the PaO_2 and F_IO_2 into the NPS Values for arterial pH, $PaCO_2$ and arterial-venous oxygen content difference ($Ca\text{-}\bar{v}O_2$) were assumed as stipulated by Nunn [1] $PaCO_2$ was then adjusted to the *in-vivo* value by adding simulated deadspace and Qs:Qt was re-estimated in the same fashion 95% limits of agreement ($LA_{95\%}$ = Bias ± 1.96 × SEM of bias) were calculated for each method

Results and Discussion: Accuracy in estimation of Qs:Qt was improved by the inclusion of $PaCO_2$ in 17 of the 20 patients The $LA_{95\%}$ in estimating Qs·Qt was −7.0 ± 3.0% when $PaCO_2$ was assumed as per the iso-shunt diagram and −4.9 ± 2.5% when $PaCO_2$ was included in the calculation. $Ca\text{-}\bar{v}O_2$ was lower in this patient group than is usually assumed in iso-shunt calculations (39 $ml\,l^{-1}$ vs. 50 $ml.l^{-1}$), partly accounting for the consistent underestimation of Qs·Qt by both methods.

Conclusion: Inclusion of the $PaCO_2$ in prediction of pulmonary shunt fraction using the NPS in hypercapnic patients improves accuracy

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A.260 Use of a model of gas exchange to infer hypoxaemia in patients with impaired *V / Q*

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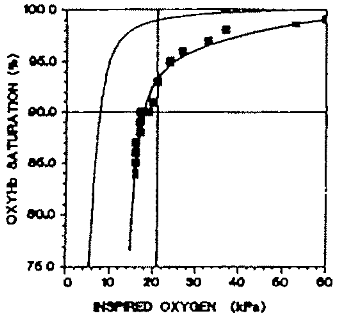
Background and Goal of Study: Commercial aircraft cruise at between 22,000–44,000 ft (1). At 44,000 ft, the cabin pressure is equivalent to that at 8,000 ft and the inspired oxygen pressure (P_1O_2) is 15.2 kPa (116 mmHg) Passengers with impaired V/Q due to acute or chronic lung disease may therefore experience profound hypoxaemia when flying.

We have used a model of gas exchange which describes low V/Q (0 ≤ V/Q ≥ 1) or shunt (V/Q = 0) from the relationship between P_1O_2 and arterial oxyhaemoglobin saturation, SaO_2 (2) We have used the model to infer hypoxaemia in patients with impaired V/Q when flying in pressurised aircraft because shunt and low V/Q have quite different effects on the shape of the curve relating P_1O_2 to SaO_2 (2)

Materials and Methods: 9 patients with chronic lung disease whose SaO_2 on air were ≤94%, were given varying concentrations of oxygen from 15–60% to breath. P_1O_2, SaO_2, ECG and heart rate were all recorded and the results put into the computer model.

Results and Discussion: A typical result is shown This patient had chronic obstructive lung disease with a SaO_2 at sea level breathing air of 93%. This patient had a shunt of 14.6% and a low V/Q effect causing a rightward shift of the curve (from the position of the dissociation curve shown on the left of the diagram) of 8.6 kPa (65 mmHg). This would have predicted a SaO_2 of 87% at 6000 ft cabin altitude, and a SaO_2 of 84% at 8000 ft cabin altitude Similar results were found in 8 other patients with chronic lung disease



Conclusions: The model enabled us to describe, in graphic fashion, the likely effect of altitude on SaO_2 in patients with impaired gas exchange This suggests that this approach may be appropriate in assessing fitness to fly as well as predicting the requirement for oxygen administration when flying.

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A.261 Assessment of regional ventilation and determination of time constants in ARDS using dynamic multiscan computed tomography

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Background: Oxygenation of patients in ARDS depends critically on the atraumatic recruitment of the alveolar space. Temporal behavior of alveolar volume changes is commonly defined using a one-compartment model of the lung Thus, one single time constant is defined In severe ARDS, we expect the presence of multiple different regional time constants Determination of different time constants could help to define optimal respirator settings and to evaluate new ventilation strategies like High Frequency Oscillatory Ventilation (HFOV). Dynamic Multiscan Computed Tomography (CT) allows for quantitative assessment of ventilated and non-ventilated airspaces with a temporal resolution up to 250 ms

Methods: With institutional approval, five anesthetized pigs (25 kg) underwent controlled ventilation in a CT unit (Somatom Plus 4, Siemens, Germany) after induction of saline lavage ARDS Dynamic multiscan CT acquisitions (slice thickness = 1 mm, high-resolution reconstruction) were performed in a single predefined transaxial plane. To determine regional time constants a single airway pressure step from 0 to 50 mbar was performed Absolute and relative lung areas exhibiting particular CT numbers were calculated planimetrically. The density range from −900 HU up to −500 HU was defined as ventilated parenchyma. A plot of the time dependent fractional increase was used to fit wash-in exponential functions to different curve sections.

Results: Two different respiratory time constants were observed in this ARDS model: One ranged from 0.9 to 1.6 s, the other one from 9.4 to 9.8 s. The slower time constant accounted for approximately 20% of the total recruitable lung area

Conclusions: Dynamic multiscan CT is an adequate method to differentiate at least two time constants in severe ARDS Slower time constants of approximately 10 s are not recruitible by conventional ventilation methods Further studies are required to evaluate new ventilation strategies like HFOV and their effects on total lung recruitment in ARDS

A.262 Measurement of regional alveolar oxygen partial pressure by helium-3 magnetic resonance imaging of the lung

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Background: Recently, MR imaging of lung ventilation using inert noble gases hyperpolarized by high-efficiency optical laser pumping has been described In this study, we aimed to demonstrate· (1) visualization of 100 mL hyperpolarized ^3He administered into the lung under controlled ventilation, and (2) *in vivo* analysis of regional intrapulmonary [O_2] based upon the property of paramagnetic oxygen to destroy ^3He polarization.

Methods: With institutional approval, five anesthetized pigs (27 kg) underwent controlled ventilation in a MRI unit (1.5 T). Using a specifically designed applicator, measured boli of ^3He were administered at the beginning of inspiration A dedicated Helmholtz coil tuned to 48.4 MHz allowed serial ^3He imaging of the lungs during inspiratory apnea. High temporal resolution could be achieved using a Turbo 2D FLASH sequence with short acquisition times of 1 second. Image interpretation was performed analysing transverse supra-diaphragmatic pulmonary cross-sections

Measurements: (i) T1 was determined from the decay of signal intensity in a series of 9 subsequent MR images (ii) The calibration of T1 versus [O_2] was performed by repeating this experiment using an end-tidal [O_2] of 0.16, 0.25, 0.35, 0.45, and varying of ^3He exposure time to oxygen at inspiratory hold (iii) The influence of perfusion on alveolar [O_2] was determined by imaging before and after induction of cardiac arrest

Results: Bolus volumina of 95 ± 4 mL hyperpolarized ^{3}He, positioned at the beginning of inspiration, were administered reproducibly. Longitudinal relaxation time T1 *in vivo* showed a linear correlation to measured end-tidal [O_2] as an effect of oxygen consumption. The absence of perfusion caused T1 derived [O_2] to lineary correlate to the FiO_2 administered

Conclusions: Visualization of small quantities of inhaled hyperpolarized ^{3}He in the lungs is technically feasible Calibration of T1-derived [O_2] values against end-tidal [O_2] and against exposure time to oxygen is possible, allowing regional measurement of intraalveolar [O_2]. Thus, T1 derived measurement of intrapulmonary [O_2] *in vivo* offers an novel instrument for the regional analysis of intrapulmonary [O_2], its time course and hence, its transfer into the blood. In addition, this method shows promise to allow detailed studies upon regional distribution of ventilation for pre- and postoperative assessment of lung function

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A.263 A comparison of three methods for measuring thoracopulmonary P-V curves in patients with acute respiratory failure

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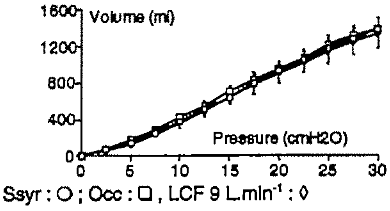
Background and Goal of the Study: Measurement of respiratory compliance is a good way to assess the severity of ARF (1). It has recently been shown that the use of an automated constant flow of 15 L/min is simple and may avoid the limitations of other methods However, pressure-volume (P-V) curves obtained with this method are shifted to the right because of resistive properties of the respiratory system (2). The aim of this study was to compare the thoracopulmonary P-V curve obtained using a low constant flow of 9 L/min delivered by a ventilator (LCF) with those obtained with supersyringe (Ssyr) and inspiratory occlusion (Occ) methods in patients with ARF

Patients and Methods: 14 patients ($PaO_2/FIO_2 = 172 \pm 92$ mmHg) were studied. Measurements were performed in ZEEP Ssyr method was performed by recording plateau airway pressure corresponding to 50 ml volume steps Occ method was performed by measuring end-inspiratory pressure corresponding to 100 ml increments in tidal volume administered in random order LCF method was performed by using a ventilator (Cesar, Taema) delivering a constant flow of 9 L/min (I/E 80%, FR 5/min) during 9.6 s. For each method, intrinsic PEEP (PEEPi) was subtracted from the P-V curve and the volume corresponding to 2.5 cmH_2O increments pressure was computed

Results: As shown, the thoracopulmonary P-V curves obtained after subtraction for PEEPi from Ssyr, Occ and LCF were similar. Slope and lower inflection point were also not significantly different between the 3 methods.



Ssyr : O ; Occ : □ , LCF 9 $L.min^{-1}$: ◊

Conclusions: Resistive phenomena is not observed when using a low constant flow of 9 L/min LCF is a simple and reliable method for measuring the thoracopulmonary P-V curve.

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TRANSFUSION AND HAEMOSTASIS

A.264 Effect of overnight sedation with lorazepam on preoperative stress in cardiac surgery

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Background & Goal of Study: This study assessed the effect of overnight sedation with lorazepam on the endocrine response to stress, measured by urinary catecholamines, plasma glucose and plasma cortisol.

Material & Methods: With ethics committee approval, 50 patients scheduled for coronary artery bypass grafting were entered into a prospective randomised study. Patients were randomised into two groups, A and B. At 20.00, the night before surgery, both groups had baseline linear visual analogue anxiety scores (LVAAS), serum glucose and cortisol levels checked. After catheterisation, 12 hour analyses of urinary adrenaline, noradrenaline and dopamine were measured. At 22 00 Group B were given 50 µg/Kg Lorazepam, Group A received nothing. At 06:00 the next morning both groups were scored for sedation and quality of sleep before receiving temazepam. At 08:00 LVAAS, serum glucose and cortisol were repeated. Non parametric data was analysed using Mann Whitney and Chi squared tests.

Results & Discussion: Measured plasma cortisol and glucose were similar over the study period in both groups Urinary noradrenaline (p = 0.04) and dopamine (p = 0.01) levels were increased in group B but urinary adrenaline levels were similar. Patients in group B had higher sedation scores overnight (p = 0.01), better quality of sleep (p = 0 0002) and less morning anxiety (p = 0.01). The observed increase in urinary catecholamines could be either a physiological response to sedation or a pharmacological response to lorazepam.

Urinary catecholamine	Group A n = 22	Group B
Adrenaline nmol/12 h	19 (15–23)	23 (19–34)
Noradrenaline nmol/12 h	96 (79–132)	150 (96–183)
Dopamine nmol/12 h	670 (514–737)	827 (624–1071)

All values shown as median (and interquartile range)

Conclusions: Improved sleep observed with lorazepam is associated with less anxiety but no reduction in the endocrine stress response. Sedation with lorazepam appears to increase the secretion of urinary dopamine and noradrenaline.

A.265 Cytokines and corticoadrenal response in elective coronary artery bypass grafting and heart transplantation

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Background and Goal of Study: The scope of cytokine biology is fascinating with widespread applications anticipated in many areas of medical science, including anaesthesia[1].

During cardiac surgery cytokines may affect the immune response and are therefore of diagnostic and therapeutic interest[2].

Our purpose in this study was to evaluate the release and relationship of cortisol, IL-6 and IL-8 in CABG and HTx.

Materials and Methods: Once we got the ethical approval, 20 male patients (aged 48–64) with coronary disease scheduled for elective CABG and other 20 for HTx (aged 45–70) were included in the study.

Blood samples for cortisol, IL-6 and IL-8 determinations were obtained in baseline conditions, at the end of the surgery and the first and second postoperative days (24 H and 48 H respectively). Aortic crossclamping time was also considered.

Aprotinin was employed as antifibrinolytic agent in both groups.

All HTx patients received same immune suppressive drugs: methylprednisolone, cyclosporine and azathioprine, without cytolytic agents

Cytokines (pg/ml) were measured by EIA method (R&D systems, Oxon, UK) and cortisol (µg%) by RIA

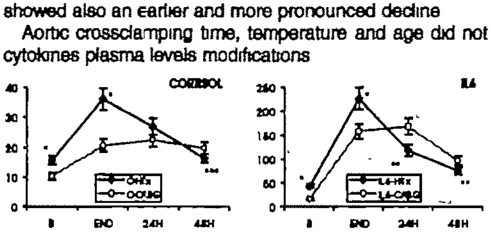
Statistical significance ($\alpha = 5\%$) was determined by ANOVA and Unpaired Student-t tests.

Results: Cortisol and interleukines baseline plasma levels were higher in the HTx group than in the CABG one.

Cytokines and cortisol plasma levels rose significantly after both surgeries and then progressively declined in the postoperative period

This elevation was more important in patients undergoing HTx and showed also an earlier and more pronounced decline

Aortic crossclamping time, temperature and age did not correlate with cytokines plasma levels modifications



Conclusions: The increase in proinflammatory cytokines (IL-6 and IL-8) plasma levels is more pronounced in patients undergoing HTx than those for CABG.

In the HTx group the cytokines release may also have been influenced by immune suppressive therapy.

The same phenomenon appears when cortico-adrenal response is considered, showing a parallelism with the inflammatory one

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A.266 Postoperative plasma concentrations of procalcitonin and C-reactive protein after cardiothoracic surgery with and without extracorporeal circulation

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Background and Goal of Study: The protein procalcitonin (PCT) is induced in the plasma of patients with severe bacterial infection or systemic inflammation As presently known, bacterial endotoxins are the main inductor of PCT To use PCT as a diagnostic tool also in the postoperative period, plasma concentrations should not substantially be induced by the surgical trauma or by extracorporeal circulation (ECC), as known by other parameters of the inflammatory response Thus, we analyzed postoperative PCT concentrations after cardiac and thoracic surgery with and without ECC in patients with a regular postoperative course

Methods: PCT and CRP was prospectively measured 5 days postoperatively in 25 patients undergoing cardiac surgery with ECC and 12 patients with thoracic surgery without ECC with a regular postoperative course and no signs of inflammation or infection

Results: During the 5-day postoperative observation period in 56% of patients undergoing cardiac surgery PCT was >0 5 μg l^{-1} (median 0 74 μg l^{-1}) and >2 0 μgl^{-1} in 8% of patients (67% and 8% after thoracic surgery, median 0 58 μg l^{-1}) PCT was not significantly different in cardiac and thoracic surgical patients (p = 0 76, MWU-test) and there was no correlation with the duration of ECC. The maximal concentration of PCT observed was 2 98 μg l^{-1} for cardiac surgery and 4 96 μgl^{-1} for thoracic surgery CRP increased in all patients observed (median 195 mg l^{-1} for cardiac surgery, 133 mgl^{-1} for thoracic surgery, p = 0 02)

Conclusion: Assessing postoperative plasma concentrations, a moderate increase of PCT (0.5–2.0 μgl^{-1}) must be encounted in the majority of patients Since up to 100-times higher concentrations of PCT are observed after bacterial infections as compared to cardiothoracic surgery, this parameter – other than CRP – obviously can be used for diagnosis of infection or inflammation also postoperatively after cardiothoracic surgery and ECC However, further studies should evaluate the sensitivity and specifity of postoperative increased PCT indicating infections or other postoperative complications

A.267 Increased von Willebrand factor after low molecular weight hydroxyethyl starch priming solution in cardiopulmonary bypass

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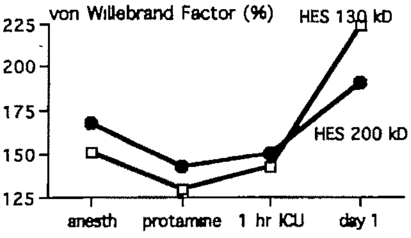
Background & Goal of Study: Most artificial colloids have a reputation of impairing hemostasis However, it was found that a 200 kD hydroxymethyl starch (HES) is as good as human albumin with regard to hemostasis during hemodilution in cardiopulmonary bypass (1), while others reported impaired hemostasis after high molecular weight (450 kD) HES infusion (2).

The availability of functional Factor VIII/von Willebrand Factor (vWF) appears to correspond importantly with hemostasis after cardiopulmonary bypass It increases the rate of intrinsic and extrinsic clotting and increases platelet adhesion to damaged capillaries After cardiopulmonary bypass with the use of albumin prime the concentration of vWF increased one hour after CPB and the first postoperative day (3)

We questioned whether two different medium molecular weight HES soultions affect vWF concentration and whether their molecular weight corresponds with hemostatic function

Patients & Methods: In a prospective randomised double blind study 49 patients received up to 3000 ml of HES with a Mw of 200 kD or with a Mw of 130 kD as heart-lung machine priming solution and as perioperative infusion Perioperatively blood samples were collected for determination of hemostatic variables Bloodloss was monitored per and postoperatively

Results: We found that vWF concentrations (Fig) as well as aPTT and platelet number increased in both groups, but significantly more in the HES 130 kD group. Blood loss was lower in the HES 130 kD group.



Conclusion: The molecular weight of HES has important effects on hemostasis A new medium molecular weight HES (HES 130/0.4) has no negative effect on hemostatic function when used in large quantities during cardiopulmonary bypass

Acknowledgements: The authors wish to thank sponsoring by Fresenius AG, Germany

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A.268 Blood transfusion and coagulation after autologous platelet-poor plasma transfusion in CABG patients

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Background: Haemodilution and the retransfusion of platelet rich plasma is used for the reduction of perioperative blood loss However, plasmatic coagulation is not supported by this method Using a platelet poor plasma (PPP) containing about 60–80% of plasma proteins we investigated the changes in plasma proteins and clotting factors after transfusion We hypothesised that the use of PPP leads to a reduced need for substitution of clotting factors and/or red blood cells (RBC) after extracorporeal circulation

Patients and Methods: 40 patients (2 f, 38 m, median 63 y, ASA III–IV) scheduled for CABG were randomised into 2 groups Group A with and Group B without haemodilution and retransfusion of PPP Anesthesia was induced with midazolam, etomidate, and sufentanil and maintained by continuous infusion of propofol/sufentanil Paralysis was achieved by pancuronium bromide Haemodilution was performed after the induction of anaesthesia with the use of HES 450 000/0 7 and a Cobe Brat 2 autotransfusion device PPP was retransfused during sternal closure Blood samples we collected at 5 min, and 7 and 14 h after retransfulon for platelet count and coagulation testing A level of <9 g/dl hemoglobin was regarded as trigger for transfusion of packed RBCs Data were statistically evaluated by ANOVA

Results and Discussion: No differences in age, bodyweight, haematocrit pre or post op, or time of extracorporeal circulation were detected between the groups Group A showed a significantly higher Quick's test (p = 0 027) and fibrinogen plasma levels (p = 0 017) after retransfusion of PPP and required less RBC transfusion intraoperatively (p = 0 025). This effect could not be found at the later timepoints, but ATIII was higher in Gr A at 14 h postop (p = 0 017) Group B required substitution of clotting factors in 3 patients and ATIII in one patient, whereas no substitution was necessary in Group A

Conclusion: We conclude that haemodilution and retransfusion of PPP leads to an improvement of coagulation parameters and reduction of RBC requirements.

A.269 Reduction of blood utilization in cardiac surgery

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Background and Goal of Study: In order to reduce homologous blood requirements, intraoperative haemodilution and aprotinin are used in cardiac surgery The aim of this study was to evaluate the efficacy of additional strategies of saving blood

Methods: This is a prospective observational study in which 89 consecutive patients were included during three months We excluded the patients with ascending aortic aneurism and emergencies. The patients were divided in four groups control group (C) (n = 39), predeposit group (PD) (n = 11), predeposit and cell saver group (PDCS) (n = 19), and a cell saver group (CS) (n = 20) In demographic data, the age was significantly lower in the PDCS group in comparison with the control and CS groups, but no other differences were found All patients received the same anaesthesia technique and the same aprotinin dosis (2 10^6 UIK) while priming the CBP The haemoglobin level was analyzed before operation and at the discharge from the hospital We evaluated the number of units of red blood cell concentrates (RBC) required during the operation and during the subsequent stay in the hospital. Median values and standard deviation are given. ANOVA was used to compare blood bank transfusion requirements between groups

Results and Discussion: Preoperative haemoglobin levels were lower in the autotransfusion groups ($p < 0\ 05$) than in the other two groups, but this is by predonation. Units of RBC transfused were 2.2 ± 1 7, 0.2 ± 0 6, 0 2 ± 0 6, 1.1 ± 1 in group C, group PD, group PDCS and group CS, respectively Requirements of RBC were significantly higher in the control group 51% of all patients were not transfused with RBC. The percentage of patients not transfused in each group were 23% in group C ($p < 0.05$ against groups PD and PDCS), 90% in group PD, 90% in group PDCS and 45% in group CS.

Conclusion: The use of predeposited autologous blood and/or cell saver decreased the blood bank consumption and increased the proportion of patients not transfused with homologous blood.

A.270 High dose aprotinin in complex total hip arthroplasty

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Background: Previous studies have demonstrated that utilization of aprotinin (AP) reduces blood loss during elective total hip arthroplasty (THA). The aim of our study was to asses the effects of AP on blood loss and the need for homologous transfusion (RBCu) in another population of patients at increased risk of blood loss, those undergoing complex THA: revision THA (rTHA) or bilateral primary THA (bTHA)

Methods: After informed consent 30 consecutive patients undergoing elective cementless rTHA or bTHA performed under combined epidural and light general anaesthesia were randomly allocated into 2 groups SF (infusion of saline. $n = 15$) and AP (infusion of aprotinin. $N = 15$). Before induction of anaesthesia a test dose of 5 ml of the study drug was administered over 2 minutes followed by a continuous infusion (loading dose 2 million KIU of AP or 200 ml of saline over 30 minutes followed by 0.5 million KIU h^{-1} of AP or 50 ml.h^{-1} of saline) for the duration of surgery Patients with impaired coagulation or renal function were excluded. Intraoperative blood loss was estimated by measuring the volume in the suction bottles and counting sponges, postoperative blood loss was measured from the surgical drains Transfusion criteria for RBCu were defined prospectively, the amount of transfused RBCu were totalled for the duration of hospitalization. Values are expressed as mean ± SD and groups were compared using the unpaired Student t test, a $p < 0.05$ was considered significant

Results: Demographic data and duration of surgery were similar in both groups. Postoperative blood loss and RBCu transfused were significantly decreased in group AP (Table 1)

Table 1

	Group SF	Group AP
Intraoperative blood loss (ml)	1236 ± 649	1094 ± 297
Postop blood loss (0–6 h) (ml)	530 ± 202	261 ± 110*
Postop blood loss (6–24 h) ml	256 ± 102	201 ± 97
Total blood loss (ml)	2021 ± 723	1576 ± 452
Total RBCu	4.2 ± 1.9	2.3 ± 2.1*

$p < 0.05$

Conclusions: This study allows us to conclude that high dose AP treatment resulted in significantly less postoperative blood loss and in a significant reduction in blood transfusion

A.271 Aprotinin administration reduces blood loss and transfusion requirements in patients undergoing total hip arthroplasty

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Background: Total hip arthroplasty may be associated with large blood loss, requiring homologous transfusion. The aim of this study was to evaluate the efficacy of aprotinin administration in the reduction of bleeding and transfusion requirements, using lower doses than recommended in other studies[1, 2].

Methods: After Institutional approval, written informed consent was obtained from 20 ASA I/II consecutive patients scheduled for primary total hip arthroplasty by the same surgical team. The patients were randomized to receive either 2×10^6KIU aprotinin during 30 minutes ($n = 10$) or normal saline ($n = 10$) in the same volume and time immediately after anaesthesia induction. Both groups received a standardized induction with fentanyl 4 μg/kg, propofol 2.5 mg/kg and vecuronium 0.1 mg/kg. Anesthesia was maintained with 60% N_2O in oxygen, isoflurane 0.5–1%, plus intermittent injection of vecuronium and fentanyl as required. Operative blood loss was determined at the end of surgery by measuring the volume of blood in the suction pump and by weighing surgical swabs. Postoperative blood loss was measured from surgical drains 24 hours later. Haemoglobin (Hb) and Haematocrit (Htc) were measured before and after surgery and when considered necessary. The patients were transfused 1 packed red cells (PRC) when $Hb < 9$ g%. Hb was determined two hours after each PRC transfusion. Enoxaparine 40 mg sc. was started 8 hours after surgery for thromboprophilaxis and given daily. Patients were daily examinated for signs of deep vein thrombosis (DVT) until hospital discharge. Results are expressed as mean ± SD Unpaired t-test and Mann-Whitney U test were used for statistical analysis A P value < 0.05 was considered statistically significant

Results: Our results are presented in the table. Bleeding reduction was 28.5% intraoperative and 30.5% postoperative No patients in the aprotinin group were transfused. No clinical DVT was observed.

Age (yr)	Aprotinin 68 ± 8	Placebo 67 ± 7
Initial hematocrit	42.1 ± 3.7%	41.0 ± 4.8%
24 h postoperative Hto	34.3 ± 3.7%	30.4 ± 3.3% (*)
Initial hemoglabin	14.3 ± 1.2 g%	14.1 ± 1.4 g%
24 h postoperative Hb	11.6 ± 1.2 g%	10.1 ± 1.2 g% (*)
Intraoperative bleeding	557 ± 165 ml	780 ± 373 ml (*)
Postoperative bleeding	265 ± 143 ml	396 ± 247 ml
Total bleeding	817 ± 147 ml	1177 ± 325 ml (*)
Patients transfused	0	3 (*)
Number of PRC transfused	0	6 (*)

(*) $p < 0.05$

Conclusion: The use of aprotinin in our protocol during primary total hip arthroplasty results in a reduction in intraoperative blood loss and less transfusion requirements. Aprotinin's dosage remains to be elucidated.

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A.272 Use of high-dose aprotinin during spinal surgery results in a reduction in both blood loss and the amount of blood transfused

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Background: Aprotinin, a serine proteinase inhibitor, has been reported to reduce blood loss significantly in patients undergoing cardiac[1] and total hip replacement surgery[2]. There was no data in the literature about the efficacy in spinal surgery associating with substantial blood loss requiring transfusion of several units of blood So we investigated the effect of aprotinin on blood loss and transfusion requirement and the potential side effects in a special type of spinal surgery

Methods: Forty patients scheduled for thoracolumbar transpedicular (TLT) fixation of spine because of spondylolisthesis were randomized to receive, in double-blind method, either aprotinin given as a bolus of 2×10^6 kallikrein inactivator units (KIU) in 30 minutes followed by an infusion of 5×10^5 KIU/h until the end of surgery or an equivalent volume of normal saline. Anesthesia and surgical techniques were standardized. Intentional preoperative normovolemic hemodilution, systemic deep venous thrombosis prophylaxis and systemic antibiotic prophylaxis were used. Intra- and postoperative blood loss and transfusion were measured. Perioperative hematocrit and hemoglobin values, renal and hepatic function were also measured. Results are expressed as the mean ± standard deviation For the statistical analysis we used Student's t test and the Mann-Whitney test.

Results: Aprotinin reduced total blood loss from 1938 ± 463 ml to 1167 ± 165 ml ($P < 0.005$) This reduction of blood loss occurred during surgery ($P < 0.005$) and postoperatively ($P < 0.001$). There were 48 units of packed red cells transfused for 12 patients in the control group and 15 units transfused for 5 patients in the aprotinin group ($P < 0.001$). One transient bronchospasm was occurred in the aprotinin group and no Incidence of deep venous thrombosis was observed in the two groups

Conclusion: The use of high-dose aprotinin combining with intentional preoperative normovolemic hemodilution results in a significant reduction in both blood loss and the amount of blood transfused.

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A.273 Blood loss reduction with aprotinin during spinal instrumented surgery

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Background & Goal of Study: Surgical procedures involving instrumented spinal fusions generally requires blood transfusion. We undertook a preliminary study of high-dose aprotinin for posterior lumbar fusion to confirm the beneficial effects of aprotinin on blood loss during spinal surgery.

Material & Methods: 20 adult patients scheduled for elective lumbar spinal surgery, were randomly assigned to two groups: group A (n =

10) received aprotinin, group B (n = 10) received placebo Surgical and anaesthesia techniques were standardised Both the surgeon and the anesthesiologist were unaware as to whether patients were receiving aprotinin or placebo.

After induction of anaesthesia, patients of group A received a subcutaneous dose test of aprotinin (50 000 kallikrein inactivator units, KIU) to refuse allergic responses; then, was given a bolus injection of 2 × 10^6 KIU over 30 min, followed by an infusion of 5 × 10^5 KIU/h until the end of surgery, with a maximum dose of 3 × 10^6 KIU. In group B was administered the same volume of normal saline according to the same protocol

We estimated perioperative blood loss by measuring the volume in the suction bottles and counting sponges (±5 ml/sponge). At the end of surgery, the surgeon evaluated bleeding on a five-point rating scale. Statistical analysis was performed using Student's *t* test and the chi-square test Results are expressed as mean ± standard deviation

Results: Total blood loss was significantly lower in group A (P < 0.01) This reduction in blood loss was clinically evident: the bleeding intensity score given by the surgeon was significantly less for the goup A patients (P < 0 01) No side effects due to aprotinin were recorded No surgical or postoperative complications were registered.

Conclusions: In our study, in patients undergoing lumbar spinal fusion, aprotinin in high doses (as recommended for cardiac surgery) resulted in a significant decrease of perioperative bleeding, with better condition of surgical field. Further investigations, could determine the optimal dosing regimen of aprotinin to reduce the requirement for blood transfusion in spinal fusion

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A.274 Aprotinin: prevalence and predictive factors for the presence of specific antibodies. A study of 520 cardiosurgical patients

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Background and Goal of Study: Aprotinin is increasingly used in all surgical disciplines as an antifibrinolytic agent either systemically or locally as a stabilizer of commercially available fibrin tissue adhesives. Both application modes can induce the formation of aprotinin-specific antibodies[1]. The presence of aprotinin-specific antibodies is considered to be a risk factor for life-threatening anaphylactic reactions at reexposure[2]. The aim of this retrospective study was to find out the prevalence of aprotinin-specific antibodies in patients scheduled for cardiac surgery

Material and Methods: The preoperative sera of 520 patients (mean age 62 ± 13 years, 68% coronary artery disease, 28% valve disease) were screened for aprotinin-specific IgG using a standard ELISA. The IgG positive sera were analyzed also for IgE employing a fluorescence enzyme immunoassay A history of previous surgical procedures was taken focussing on aprotinin-preexposure and surgical procedures

Results and Discussion: 22 of 520 (4%) patients were positive for aprotinin-specific IgG antibodies Only three of these (14%) had a documented preexposure Ten patients (10/22) had undergone relevant surgical procedures either in cardiovascular surgery (4/10), or in otorhinolaryngology (ENT, 3/10), or in both (2/10), or in traumatology (1/10) Aprotinin was administered in all patients. One patient having had a recent systemic preexposure in cardiac surgery, presented now with a severe anaphylaxis She was the only being preoperatively positive for both, aprotinin-specific IgG and IgE antibodies, as revealed by retrospective analysis. Surgical history, especially cardiovascular and ENT procedures, seems to be more indicative for aprotinin-preexposure than documentation in the chart. A possible explanation may be insufficient documention of aprotinin use, particularly as a component of fibrin sealants.

Conclusion: In patients with this anamnestic profile measures to avoid anaphylactic reactions are stringent at reexposure to aprotinin.

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A.275 Influence of aprotinin in the proinflammatory cytokine response to elective cardiopulmonary bypass

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Background and Goal of Study: Proinflammatory cytokines have been implicated as mediators of multiorgan disfunction after CPB[1,2] On the other hand, aprotinin which is frequently used as antifibrinolytic agent in coronary artery bypass grafting (CABG) may have immunologic effects

The purpose of this study was to evaluate the influence of aprotinin on the release of IL-6, IL-8 and TNF-α during CABG and in the earlier postoperative period

Patients and Methods: After institutional ethical committee approval, 36 patients (aged 48–64), undergoing CABG were randomized in two groups with or without aprotinin· Control group (CG) n = 18 and Aprotinin group (AG) n = 18, respectively. There were no differences in age, weight, sex, corporal surface and anaesthetic-surgical management

Blood samples for IL-6, IL-8 and TNF-α determinations were obtained in baseline conditions, at the end of surgery, 24, 48 and 72 postoperative hours. Haemodinamic data, aortic crossclamping time and temperature were also considered All cytokines were measured by enzyme immunoassay method (R&D systems, Oxon, UK)

Results were shown as (MEAN,SD) and statistical significance (p < 0 05) was determined by ANOVA and Unpaired Student-t tests

Results: Proinflammatory cytokines plasma levels rose significantly in both groups (p < 0 0001 for IL-6 and IL-8, p < 0 05 for TNF-α) at the end of surgery and progressively declined during the following postoperative days TNF-α showed the less remarkable modifications

There was no correlation between cytokines increase and aortic crossclamping time or temperature

In the aprotinin group, the increase in plasma levels of IL-6 (24 h) and IL-8 (24 h & 48 h) were significantly lower compared with the control group There were no differences in TNF-α plasma levels in the aprotinin group

pg/ml	IL-6 (CG)	IL-6 (AG)	IL-8 (CG)	IL-8 (AG)	TNF-α (CG)	TNF-α (AG)
Baseline	15 1, 23 3	8 5, 3 3	63 6, 27	55, 14 1	7, 2 2	7 3, 1 8
24 h	235 6; 33 9*	158 4, 50*	156 2, 82 2*	100, 47 8*	10 2, 3 6	9 5, 4 1
48 h	188 2, 49	169 4, 58	150 1, 53 2*	82 8, 47 2*	9 5, 3 9	7 8, 2 8
72 h	107 3; 51 5	97 4, 45 3	88 5, 40 3	68 3; 32 5	9 1, 4 6	8, 2 6

* = *p < 0 05*

Conclusions: Proinflammatory cytokines IL-6 and IL-8, specially the former, are good indexes to evaluate stress response to CPB

Aprotinin may influence the release of proinflammatory cytokines.

The role of aortic crossclamping time and temperature in the release of cytokines looks unclear

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A.276 Perflubron emulsion delays blood transfusions in orthopaedic surgery

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Background and Goal of Study: Fluorocarbon emulsions have been proposed as temporary artificial oxygen (O2) carriers [1] Aim of the present study was to compare the effectiveness of perflubron emulsion (Alliance Pharmac. Corp, San Diego, CA and R W Johnson Pharmac Research Inst., Zurich, Switzerland and Raritan, NJ) with the effectiveness of autologous blood or colloid infusion in reversing physiologic transfusion triggers.

Materials and Methods: With approval of the local Ethical Committees and written informed consent 147 patients undergoing elective orthopaedic surgery were enrolled in this multinational, multicenter, randomised, controlled, single-blind, parallel group study Patients were monitored with radial artery and pulmonary artery catheters and underwent acute normovolaemic haemodilution (ANH) preoperatively to a target haemoglobin of 9 g/dL During the first stage of operation an inspiratory O2 fraction (FiO2) of 0.40 was used Patients were kept normovolaemic throughout surgery by maintaining their post-ANH PCWP Patients were randomised into one of four treatment groups when reaching a physiologic transfusion trigger such as tachycardia (heart rate >125% of post-ANH or >110 bpm), hypotension (mean arterial pressure <75% of post-ANH or ≥60 mmHg), cardiac output >150% of post-ANH or mixed venous PO2 < 38 mmHg. Treatment in the four groups were 450 ml autologous blood harvested during ANH with FiO2 = 0 40 (AB), 450 ml colloid (gelatin or hydroxyethyl starch) with FiO2 = 1.0 (COL), 0.9 g/kg Perflubron with colloid (total = 450 ml) with FiO2 = 1.0 (P0.9) and 1.8 g/kg Perflubron with colloid (total = 450 ml) with FiO2 = 1 0 (P1 8) The primary endpoint was duration of transfusion trigger reversal A secondary endpoint was percentage of transfusion trigger reversal The logrank test and Fisher's exact test were used (p < 0.05) Data are median (95% CI).

Results: Patient characteristics and baseline data were comparable between treatment groups Perflubron emulsion was well tolerated. Duration of reversal and percentage of reversal were significantly different between the P1.8 and either control group (AB and COL).

	AB	COL	P 0 9	P 1 8
Duration [min]	55 (30–70)	30 (27–60)	59† (40–90)	80*†
Reversal [%]	60	76	82	97$^{\$\dagger}$

* = sign vs AB (adj for multiple testing), † sign. vs COL, $^{\$}$ = sign vs AB

Conclusion: Perflubron emulsion (1 8 g/kg) is more effective than autologous blood or colloid infusion in reversing physiologic transfusion triggers

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A.277 Effect of acute normovolaemic haemodilution on allogenic blood transfusion during cardiac surgery: a meta-analysis

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Background and Goal of Study: Acute normovolaemic haemodilution (ANH) is used during surgery as a means of avoiding transfusion of allogeneic blood [1] Meta-analysis (MA) is a quantitative review procedure in which a large collection of results from individual studies are statistically analysed [2] This study examined the efficacy of ANH as a blood conservation technique in cardiac surgery using MA.

Material and Methods: A bibliography was assembled by searching the Medline database coupled with cross-referencing from 1966–1997. Human studies in patients undergoing cardiovascular surgery were selected according to study N, control group and reported data. The effect of ANH on transfusion of allogeneic blood products (Sub-study A) and on surgical blood loss (Sub-study B) was examined using Meta-analysis Programs, Version 4 3 (weighted integration and random effects model). $p < 0.05$ was used for statistical significance.

Results and Discussion: Of the 122 publications retrieved, 22 focused on cardiovascular surgery in humans, viz. cardiac surgery; $n = 14$, vascular surgery; $n = 8$. Volume of sequestered whole blood ranged from 450–2100 mLs and was either heparinized or collected in citrate anticoagulant For Sub-study A, 7 eligible trials (sample size – 723) reported that allogeneic blood transfusion requirements were decreased in patients undergoing ANH (mean effect size = 2 0 ± 0 09, $p < 0.001$, homogeneity Q = 676 1, $p < 0.001$; sampling error variance = 1 13%. For Sub-study B, 5 eligible trials (sample size – 351) reported that blood loss decreased in patients undergoing ANH (mean effect size = 0 8 ± 0 11, $p < 0.001$, homogeneity Q = 415.8, $p < 0\ 001$; sampling error variance = 1%). A Fail-Safe N exceeded 25 for both sub-studies

Conclusion: Although these results suggest that ANH is an effective blood conservation technique, the population sample reported above does not meet a test of homogeneity. Over 75% of the variance was due to systematic factors, i.e. study characteristics and variable not identified or reported in studies Therefore, additional trials that tightly control patient sampling and study design are required.

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A.278 Pre-autologous blood donation: comparison of red blood cell apheresis and standard whole blood donation in total hip arthroplasty

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Goal: The aim of this study is to evaluate the efficacy and safety of a new PAD technique: Red Blood Cell Apheresis (RBCA), performed 25 days prior to surgery, in comparison with Standard Whole Blood PAD (SPAD). A preliminary study has shown that when Red Blood Cell Apheresis is performed 2 days prior to surgery, it is not more effective than passive intraoperative hemodilution (1). From a quality standpoint, red cell concentrates obtained by apheresis 30 days prior surgery are similar to red cells obtained by manual whole blood collection (2) Efficacy is judged by allogenic blood transfusion reduction and safety by tolerance during and after apheresis.

Patients and Methods: The prospective, multicenter clinical trial included 60 consenting patients (age 18 to 78 years, Hb > 12 g/dl, weight >55 kg, ASA status 1 or 2), scheduled for THA, randomized in 2 groups (RBCA or SPAD) Red Blood Cell Apheresis was performed on a MCS-3P device (Haemonetics® Braintree, MA), by hemodilution at the Blood Bank 25 ± 5 days prior to surgery: only erythrocytes were removed and plasma was reinfused immediately. By reducing haematocrit (Hct) between 30 and 32%, 2 or 3 RBC units were collected from each patient in this group. In the Standard PAD group, autologous whole blood was collected every week up to a maximum of 4 units. All patients received 200 mg of iron sulfate Immediate and late side effects of both procedures were recorded The transfusion goal was set at Hct = 30% from recovery room (D + 3 h) until discharge (D + 8) Results are shown as mean ± SD. Wilcoxon procedure was used for statistical analysis

Results: The 2 groups were similar in age, weight, gender and Hct rate from D + 3 h until D + 8. Early side effects were three mild citrate reactions in RBCA group and one hypotension in SPAD group. Late side effects, such as mild asthenia or light-headedness were not different in the 2 groups.

	RBCA	SPAD
Allogenic transf	*0*	*0*
Autologous transf (ml)	510 ± 161	493 ± 178
RBC collected/patient (ml)	630 ± 167	555 ± 141
Total Hb collected/patient (g)	128 ± 35	*105 ± 24
Hct (%)/Hb(g/dl) at D-1	39 ± 3/13 ± 1*	37 ± 4/12 ± 1

Conclusion: A single RBC Apheresis performed 25 days prior to surgery is as efficient as Standard PAD in avoiding allogenic transfusion for primary THA. Collection of 3 RBC units in the same course by apheresis is as well tolerated as 3 or 4 sequential whole blood collections. These results are in accordance with previous data about safety (3). This new procedure results in lower frequency of donations and reduced laboratory testing. Furthermore, an enhanced erythropoiesis may be expected.

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A.279 Oral iron supplementation increases erythropoiesis in autologous blood donors

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Background and Goal of Study: Most autologous blood donors receive oral iron supplementation but the benefit of this therapy is uncertain (1) We compared the efficacy of a standard oral iron supplementation with that of a combined oral plus intravenous iron supplementation in patients undergoing weekly autologous blood donation.

Materials and Methods: This was a single-center, randomized, double-blind, placebo-controlled, parallel-group study One hundred eight iron-replete patients who were scheduled for donation of 3 units of autologous blood at weekly intervals were randomly assigned to receive, in a double-blind fashion, no iron supplementation (placebo), oral iron supplementation (285.6 mg of elemental iron/day), or oral plus intravenous iron supplementation (285 6 mg of elemental iron/day orally + 102.5 mg of elemental iron/week intravenously) RBC production (over baseline production) during the 21-day study period was determined by the total volume of RBCs donated minus the change in circulating RBC volume between the first donation and the end of the study period (2) Data are presented as mean ± standard deviation. RBC production amongst the study groups was compared by one-way analysis of variance followed by Scheffe's test for pairwise comparisons. $P < 0.05$ was considered significant

Results and Discussion: RBC production during the study period did not differ significantly between the two iron-supplemented groups (oral iron group, 331 ± 124 ml; oral plus intravenous iron group, 315 ± 137 ml) RBC production in either iron-supplemented group was significantly greater than in the placebo group (220 ± 124 ml; $p < 0.01$ vs oral iron group, and $p < 0.05$ vs oral plus intravenous iron group).

Conclusion: Oral iron supplementation increased the production of RBCs in autologous blood donors compared with placebo. Additional intravenous iron (102.5 mg of elemental iron once weekly) did not further augment RBC production. This is the first study that demonstrates the efficacy of oral iron supplementation in increasing erythropoiesis in iron-replete autologous blood donors.

Acknowledgement: This study was supported in part by a grant from Rhône-Poulenc-Rorer (Koln, Germany)

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A.280 Postoperative blood retrieval and transfusion in total knee arthroplasty

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Total joint arthroplasty is a procedure usually accompanied by significant blood loss requiring transfusion Risks of transfusion include the transmission of viric illness and other important side effects (1) Alternatives to homologous banked blood transfusions are. Predonated autologous transfusion, intraoperative blood salvage, haemodilution and postoperative blood salvage The aim of our study is demonstrate the efficacy and safety of a postoperative blood salvage system in total joint arthroplasty and the reduction of homologous blood transfusion

Methods: We studied prospectively 100 patients undergoing Total Knee Arthroplasty (TKA) using ConstaVac CBCII postoperative blood salvage system, and we compare them to 40 patients undergoing TKA using a standard drainage system (Control Group) All patients received subarachnoidal anaesthesia We analyse the evolution of preoperative, postoperative immediately and at 24 hours postoperatively blood parameters. Amount of salvaged blood, values of haemoglobin of this blood and the volume of homologous transfusion and adverse reactions during and following transfusions were also recorded Exclusion criteria were chronic liver diseases, coagulation disturbances and patients with history of infection and malignant pathology Operative technique with tourniquet, length of surgery and postoperative management were identical in all patients

Results: We included 140 consecutive patients, 40 in control group (CG) and 100 in the study group (SG)

All patients were similar in gender, age, weight and ASA clinical status. Preoperative blood parameters were similar between groups The amount of blood retrieved and transfused averaged 660 ± 275 (250–1800) ml. Homologous blood transfusion was averaged 315 ± 325 ml in CG and 21 ± 108 ml in SG ($p < 0.000001$) Values of haemoglobin at 24 hours were 10 6 ± 1.24 g/dl in CG vs 11.8 ± 1 6 g/dl in SG (p = 0 00004)(2) No secondary effects were recorded

Conclusions: This study indicates that a postoperative blood salvage system safely and effectively reduces the amount of homologous blood requirements and sustains higher hemoglobin levels after operation without adverse effects in patients undergoing TKA

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A.281 Intraoperative autotransfusion combined with irradiation of the washed erythrocytes for tumour surgery: experience with 30 patients

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Introduction: As shown by Hansen et al (1) tumor surgery is no longer a contraindication for the intraoperative auto-transfusion, under the condition, that washed erythrocytes are irradiated with a tumoricide dose of 50 Gy to eliminate the always present vital malignant cells.

Method: 30 Patients scheduled for major tumor surgery with a mean blood loss of 2580 ± 1930 ml had 670 ± 360 ml of washed and irradiated (50 Gy) erythrocytes retransfused Repeated measurements of free hemoglobin, lactate dehydrogenase (LDH) and serum potassium as markers of hemolysis were taken during the first 3 hours postoperatively and the patients were closely observed for adverse effects Acute normovolemic hemodilution (ANH) and individualized transfusion limits were additional strategies to reduce allogeneic blood donation

Results: Free hemoglobin levels were <0 8 g/l in all tests, potassium and LDH always within normal limits One Patient developed sepsis due to bacterial over-growth of the retransfused blood. Allogeneic transfusions in the group of 23 total prostatectomies were reduced from 5 9 ± 6 7 to 3 5 ± 3.4 units (by 41%) compared to a retrospective control group (n = 90)

Conclusions: Manipulations of blood products (e g. taking laboratory tests) bear the danger of bacterial overgrowth and should be avoided Irradiation of washed erythrocytes does not result in clinically relevant hemolysis The combination of this technique with ANH and the introduction of individualized transfusion limits reduced allogeneic transfusions at our institution significantly

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A.282 Platelet activation during and after major vascular surgery

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Background and Goal of Study: Postoperative platelet activation plays a role in cardiac events following surgery in CAD patients Accordingly, we have performed a prospective study to assess platelet reactivity during and after abdominal aortic surgery

Materials and Methods: After IRB approval and informed consent, 17 patients (mean age 67 yo) were studied. Anesthesia was induced by propofol, sufentanil, and atracurium and maintained with isoflurane Patients treated with aspirin or receiving platelet or plasma transfusion were excluded. Blood samples were drawn before induction (T1), one hr after incision (T2), one hr after extubation (T3), 24 hrs postoperatively (T4), 48 hrs postop (T5), and at day 7 (T6) The following tests were performed at all steps of measurements platelet count, arachidonic acid (AAA) and ADP-induced (ADPA) platelet aggregation and flow cytometry for CD62 (P selectin, alpha granule membrane glycoprotein expression). This glycoprotein is closely related to platelet activation

Results and Discussion: A significant increase in ADP-induced aggregation was observed postoperatively at T4 and T5 and returned to control at T6 indicating an increased platelet aggregability A trend was also observed with arachidonic acid-induced aggregation This was not associated with a change in flow cytometry suggesting that platelet are not activated but are prompt to be activated

	T1	T2	T3	T4	T5	T6
Platelets (G L^{-1})	210 ± 61	186 ± 69	174 ± 60	163 ± 43	156 ± 52	340 ± 105
AAA (%normal)	96 ± 29	98 ± 45	101 ± 67	145 ± 85	137 ± 75	100 ± 12
ADPA (%/normal)	103 ± 29	112 ± 38	104 ± 33	120 ± 29*	127 ± 28*	93 ± 22
CD62 (%/normal)	96 ± 38	75 ± 14	71 ± 16	77 ± 15	92 ± 30	70 ± 7

Statistical analysis Results are expressed as % of normal subjects values – Mean ± SD, *$p < 0.05$ versus T1

Conclusions: Post-operatively, in vascular surgery patients, circulating platelets are not activated even if they are activable as demonstrated by flow cytometry However platelet aggregability is increased demonstrating their high sensitivity to any activation (including stress) These results must be taken into account to limit postoperative cardiac events in vascular surgical patients

A.283 Intracellular storage of hydroxyethyl starch in human endothelial cells *in vitro*

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Hydroxyethyl starch (HES) is a colloid commonly used for volume replacement during shock or hypovolemia and for hemodilution in order to increase microcirculatory blood flow In man, intracellular storage of HES has been demonstrated in macrophages and in keratinocytes of the skin after long time hemodilution of patients with sudden deafness. The endothelial cell is a critical component in the pathogenesis of shock or reperfusion injury, diseases commonly treated with HES We therefore studied the effects of different concentrations of this colloid on the appearance and kinetics of ingestion and intracellular storage of HES molecules in human umbilical venous endothelial cells (HUVEC) in vitro

Methods: Confluent HUVEC were incubated for various periods of time (1–72 hours) at 0 5–20 mg/ml with FITC conjugated HES 200/0 5 (FITC-HES). The amount of intracellular stored HES was quantified by the emitted fluorescence of the FITC-HES molecules, using flow cytometry The morphology of intracellular storage was studied by fluorescence microscopy Cells with medium alone, FITC-supplemented medium and FITC-supplemented medium with unconjugated HES 200 served as controls To evaluate the long time storage, a further group of cells was incubated with FITC-HES and afterwards cultured for 5 days in FITC-HES free medium

Results: Incubation with FITC-HES resulted in a remarkable degree of intracellular storage in HUVEC Intracellular stored HES showed a typical morphology of numerous intracellular, fluorescent vesicles The degree of storage seemed to be both, time and concentration dependent The morphological picture was caused by the HES molecules themselves, since incubation with FITC-supplemented medium, either with or without unconjugated HES resulted in a completely different morphological picture This excluded the possibility that HES leads to vesicle formation of other components than the HES molecule itself The storage of HES molecules seems to be irreversible, since the emitted fluorescence after 5 day culture in HES-FITC free medium decreased only to a little degree, which can be contributed to the well known bleaching of FITC under the conditions of 37°C in an incubator

Conclusion: HES is stored in a concentration and time dependent manner in endothelial cells Once stored, the cells are not able to reduce the stored amount of HES molecules anymore Because of cumulative effects, application of low concentrations of HES over a long period of time results in a more pronounced storage then a short timed therapy does, even when high doses are applied Regarding the magnitude of storage, it has to be hypothesized that functional changes in these cells are likely to occur Whether this hypothesis holds true and whether the possible functional changes can be beneficial during reperfusion is under investigation in our labaratory

A.284 Hydroxyethyl starch impairs *in vitro* coagulation

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Background: Haemostatic mechanisms are affected by artificial colloids; hydroxyethyl starch (HES), in particular, may be detrimental to haemostasis[1, 2].

Methods: In a crossover study with ten volunteers Ringer's acetate, 6% low molecular weight HES (MW 120 000/molar substitution ratio 0.7), 10% low molecular weight HES (M_W 200 000/0.5) and 6% high molecular weight HES (M_W 400 000/0.7) or 4% albumin was added to venous blood samples to make either 20 vol.% or 50 vol.% concentrations of each of the solutions. Samples were analyzed by thrombelastography (TEG). The differences were tested with Kruskal-Wallis test

Results: All HES solutions at 20 vol.% concentration impaired haemostasis as demonstrated by decreased clot formation rate (α-angle) and maximum amplitude (MA) In contrast, Ringer's acetate and albumin improved coagulability at 20 vol.% concentrations. Coagulation time (r + K) was prolonged at 50 vol.% dilutions of all solutions. The median r + K was greater with HES 400 ($p < 0.05$) and HES 200 (N.S.) than with HES 120

Conclusion: We conclude that HES at 20 and 50 vol.% concentrations has an adverse effect on *in vitro* measures of coagulation. A 50% dilution with high molecular weight HES seems to impair coagulation more than low molecular weight HES. Ringer's acetate and albumin at 20 vol.% caused a hypercoagulable state by an interaction with or activation of coagulation factors On the other hand, the decreased coagulability at 50 vol.% concentration was probably a dilutional effect.

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A.285 Potato starch derived hydroxyethyl starch (200 000/0.5) compromises *in vitro* blood coagulation more than corn starch derived hydroxyethyl starch (200 000/0.5)

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Background & Goal of Study: Hydroxyethylstarch (HES) solutions were traditionally derived from corn starch. Recently, a new potato starch derived HES solution was developed. The goal of this study was to compare the effects of potato starch derived (pHES) and corn starch derived HES (cHES) on In vitro blood coagulation

Materials & Methods: With approval of the local ethics committee and written informed consent, 10 ml blood was collected from 80 surgical patients. Exclusion criteria were known coagulation disorders, renal and liver diseases and drugs interfering with blood coagulation. Blood samples were randomised to a 30% or 60% hemodilution group (30%HD, 60%HD) and subsequently diluted 30% and 60% in vitro with 0.9% saline, cHES 200'000/0.5 (HAES-steril® 6%, Fresenius Pharma, Stans, Switzerland) and pHES 200'000/0.5 (Infukoll® HES 6%, Serum-Werk Bernburg, Bernburg, Germany). Blood coagulation was assessed using thrombelastography (TEG) [1]. TEG tracings were analysed in terms of reaction time (r, normal = 12.0 + 2.3 mm), coagulation time (k, normal = 4.2 ± 1.6 mm), maximum amplitude (MA, normal = 63.5 ± 4.5 mm), angle α (α, normal = 60.2 ± 6.7°) and coagulation index (CI = −0.3258·r − 0.1886 k + 0.1224 MA + 0.0759 α − 7.7922, normal = 0 ± 2) [2] Parameters of hemodiluted blood were analysed using repeated measures analysis of variance with Greenhouse-Geisser correction P < 0.05 was considered statistically significant. Data are mean ± SEM

	Native	30% HD		60% HD	
		cHES	pHES	cHES	pHES
n	80	40	40	40	40
r	9.3 ± 0.7	10.4 ± 0.9	10.6 ± 1.0*	10.9 ± 0.7	12.2 ± 0.9*
k	3.5 ± 0.2	6.1 ± 0.4	6.7 ± 0.5*	14.4 ± 0.8	15.4 ± 0.8*
MA	67.6 ± 0.7	52.4 ± 1.1	51.6 ± 1.2*	36.8 ± 0.9	36.1 ± 0.9*
α	68.3 ± 1.0	56.0 ± 1.4	54.5 ± 1.7*	37.5 ± 1.1	34.7 ± 1.2*
CI	2.0 ± 0.4	−1.7 ± 0.5	−2.1 ± 0.6*	−6.7 ± 0.4	−7.6 ± 0.5*

*Significantly different ($p < 0.05$) from cHES during HD

Results: Hemodilution (HD) with both cHES and pHES compromised blood coagulation significantly Results are shown in the table

All values for cHES and pHES (except r at 30%HD) are significantly different from native. HD with pHES compromised blood coagulation significantly more than HD with cHES. This is evidenced by a greater increase of r and k and a more pronounced decrease in MA, α and CI during HD with pHES than with cHES

Conclusion: In vitro blood coagulation is more seriously compromised by potato starch derived HES than by corn starch derived HES

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A.286 Preoperative hypervolaemic haemodilution with 6% low-molecular-weight hydroxyethyl starch: effect on some coagulation factors

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Background and Goal: Preoperative haemodilution decreases transfusion requirement from major surgery[1] However the used dilutant might interfere with the activity of coagulation factors and thus increase the effect of their dilution The 6% LMW-HES Elohès™ did not depress factor VIII activity[2] and seemed safe for hypervolaemic haemodilution[3]. Therefore, this study described the effect on coagulation of Elohès™ used for acute hypervolaemic haemodilution in patients operated for colectomy under general anaesthesia (isoflurane/N_2O, fentanyl, vecuronium).

Methods: After induction of anaesthesia and measurement of CVP and invasive arterial pressure, Elohès was infused until the hematocrit (Ht) reached 30%

Arterial blood was sampled before and after dilution for blood gases (ABG), albumin ([alb]), Ht, coagulation studies: thrombin time (TT), APTT, Quick time and measurement of coagulation activity (Act) of. fibrinogen (I), prothrombin (II), factors VII, VIII, X The antigenic concentration ([Ag]) of these factors was also measured and related to Act to detect interference from Elohès

For this purpose, the ratios Act/[Ag] of each factor was calculated before and after dilution and compared using non-parametric tests. Results are given as· median [interquartile range].

Results & Discussion: Ten ASA 1 & 2 patients were studied. age = 58.5 [45; 66] yrs, BMI = 24.8 [21; 27] kg.m^{-2} Immediately preoperative Ht = 37.7 [35.6, 42.4]% and [Alb] = 37 [34.5; 41] g L^{-1}

The infusion of 11.9 [10; 13.6] mL kg^{-1} of Elohès™ gave

(a) Ht = 30.6 [28.5, 30.8] % [Alb] = 29 [26.5; 30] g.L^{-1}

(b) No modification in ABG, heart rate, mean arterial pressure but CVP increased +45 [20, 75]%

(c) TT, APTT, Quick time remained normal

(d) Parallel decrease in [Ag] of each factor and in [Alb]: −25 [−34.3, −19] %.

(e) Non significant and very small variations in Act/[Ag] of each factor (see table)·

Act/[Ag]	I	II	VII	VIII	X
Variation	−1.9	−1.5	0	−1.3	−2.2
%	[−5.5; 1.7]	[−2.4; 5]	[−2, 2.4]	[−13, 13]	[−2.4, 6.1]

Conclusion: Elohès infused for hypervolaemic haemodilution at approximatively 12 mL kg^{-1} did not have a direct effect on the activity of the studied coagulation factors.

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A.287 Safety and tolerance of a novel formulation of hydroxyethyl starch (HES 130/0.4) in patients undergoing autologous blood donation with isovolaemic volume replacement

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Background and Goal of Study: HES 130/0.4 is a novel formulation of hydroxyethyl starch with a mean molecular weight of 130,000 daltons and a molar substitution ratio ranging between 0.38 and 0.45 HES 130/0.4 has an intravascular half-life similar to that of current medium molecular weight hydroxyethyl starchs (HES 200/0.5) but is more rapidly and more completely excreted by the kidneys once the solution has left the intravascular space. We evaluated the safety and tolerance of HES 130/0 4 in the autologous blood donation setting HES 200/0.5 (HAES-SterilTM 6%, Fresenius, Bad Homburg, Germany) served as control

Materials and Methods: This was a single-center, controlled, randomized, double-blind, parallel-group, phase II clinical trial Sixty patients, ASA physical status class I–III, scheduled for elective surgery, were randomly assigned to receive, within 15 min and simultaneous to withdrawal of a unit (500 ml) of blood, an intravenous infusion of 500 ml of either HES 130/0 4 or HES 200/0.5. The concentration of either solution was 6 percent. Heart rate and blood pressure were measured oscillometrically before as well as 0, 30, and 60 min after blood donation. Blood samples for laboratory studies (haematology and clinical chemistry) were collected before and 60 min after donation and infusion of the study material. Patients were followed up for 24 h by means of a patient diary. Metric variables were compared by calculating 95% confidence intervals (CIs) for differences between groups Dichotomous variables were compared by Fisher's exact test. P < 0 05 was considered significant

Results and Discussion: There was no significant difference amongst the groups with respect to anthropometric data and medical history All patients completed the study according to protocol. No adverse events were observed during the monitoring period in the blood bank. At any time, heart rate, blood pressure, and laboratory data did not differ significantly between the HES 130/0.4-treated patients and their HES 200/0.5-treated controls (95% CIs included zero). The frequency and type of side effects (e g., dizziness, fatigue) recorded in the patient diaries (24 h after blood donation and infusion) were similar for both groups

Conclusion: Both HES 130/0.4 and HES 200/0.5 in a 1 1 volume ratio to blood loss effectively prevented hypotension (>20% decrease in systolic blood pressure from baseline) during and until 60 min after blood donation. Without intravenous volume replacement, such events may occur in as many as 50% of autologous blood donors (1) The tolerance of HES 130/0 4 was as good as that of HES 200/0 5 was

Acknowledgement: This study was supported by a grant from Fresenius AG (Bad Homburg, Germany)

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A.288 Factors involved in the perioperative adrenomedullary response to open heart surgery

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Background & Goal of Study: Adrenomedullin (AM) is a recently identified vasodilating peptide Plasmatic AM levels are increased in different cardiovascular diseases (systemic or pulmonary arterial hypertension, heart failure, etc) We (1) and others (2) have demonstrated that AM increases during the perioperative period The aim of this study was to assess if basal hemodynamic parameters predict the AM response to open heart surgery

Material & Methods: We measured preoperative hemodynamic parameters and AM levels (RIA) in a group of 29 patients submitted to open heart surgery (14 valvular replacement, 10 coronary bypass and 5 valvular replacement plus coronary bypass) before the start of anesthesia, before the start of CPB, 20′ after the start of CPB, at the end of CPB, at the end of surgery, and 24 hours after the start of surgery Anesthesia was induced and maintained with sucesive doses of midazolam and fentanyl Muscle relaxation was achieved with vecuronium bromide

Results & Discussion: AM levels at the different times were 214 ± 287, 194 ± 286, 173 ± 206, 350 ± 367(*), 637 ± 711(*) and 618 ± 785(*) pg/ml, (*) p < 0 01, p < 00001, p < 0.0001 respectively, Friedman test followed by Wilcoxon test Basal AM levels were increased compared with a control healthy group Basal AM levels correlated significantly with systolic pulmonary pressure SPP (rs = 0.46 p = 0.013) and PCWP (rs = 0.44 p = 0 02), but not with other hemodynamic parameters When we compared those patients with ejection fraction (EF) < 40% with those >60%, AM levels were higher in the group with EF < 40 at the end of CPB and at the end of surgery (p < 0.03 and < 0 05 respectively).

Conclusions: Basal preoperative AM correlates with SPP and PCWP AM levels increase after the end of CPB, and the increase is higher in those patients with less EF.

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A.289 Measurement and correction of ionized plasma magnesium during cardiopulmonary bypass

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Background and Goal of Study: Determination of plasma magnesium during and after cardiopulmonary bypass (CPB) is receiving increasing interest, not least because of the apparent association between hypomagnesaemia and cardiac arrhythmias (1). Magnesium (MgSO4) is frequently administered empirically to these patients The recent introduction of ion-selective electrodes (2) has facilitated serial measurement of ionised plasma magnesium [iMg2+] reflecting the active form of magnesium (3) The aim of our study was to determine levels of [iMg2+] in patients presenting for CPB and to correlate these with the dose of MgSO4 administered intraoperatively to maintain a normal or high [iMg2+] (ref range 0 54–0 67 mmol/l)

Materials and Methods: A pilot study involving 35 patients undergoing coronary artery bypass grafting (CABG) was performed [iMg2+] was determined using an ion-selective electrode (type Nova Biomedical) before, during (three samples) and after CPB When [iMg2+] was found to be low or declining steadily, MgSO4 10 mmol was administered intravenously

Results: 34 out of 35 patients displayed low [iMg2+] before initiation of CPB (mean 0 49 mmol/l, SD 0 03) Administration of MgSO4 10 mmol resulted in a mean rise of [iMg2+] by 0 24 mmol/l (SD 0.07) However, a continuous steady decline resumed and nine patients required a second dose of MgSO4 10 mmol The mean dose of MgSO4 administered was 12 6 mmol.

[iMg2+] M + SD	MgSO4 10 mmol	MgSO4 20 mmol
Pre CPB	0 49 ± 0 03	0 48 ± 0 03
During CPB, 1	0 70 ± 0 11	0 73 ± 0 11
During CPB, 2	0 70 ± 0 06	0 63 ± 0 07
During CPB, 3	0 66 ± 0 06	0.86 ± 0 18
Post CPB	0 59 ± 0 04	0 84 ± 0 13

Discussion: Our study demonstrated that a large proportion of patients presenting for CABG had abnormally low [IMg2+] These levels were corrected by the intravenous administration of MgSO4 10–20 mmol This may have implications for the prevention of postoperative cardiac arrhythmias

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A.290 Heparinase reverses the inhibition of platelets by heparin in patients undergoing cardiopulmonary bypass

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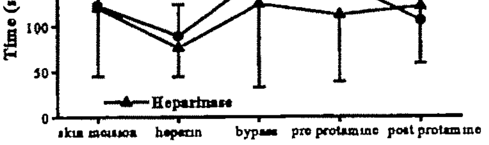
Introducton: Heparin, necessary for systemic anticoagulation during cardiopulmonary bypass (CPB), affects platelet function. Proaggregatory effects occur in 8.6%, mild to moderate inhibition in 58 6%, and severe inhibition in 32.8% of patients undergoing CPB (1). Protamine for reversal of heparin after CPB further worsens platelet function additionally, by causing thrombocytopenia and decreasing platelet aggregability (2) Heparinase, an enzyme isolated from *Flavobacterium heparinum,* is a possible alternative to protamine. In contrast to protamine heparinase seems to have minimal effects on platelets (3) The aim of the study was to test the hypothesis that heparinase is able to reverse inhibiting effects of heparin on platelet function, we measured platelet function in patients undergoing cardiac surgery

Methods: With local Ethics Committee approval and informed consent, 27 patients undergoing CPB were investigated. Patients were given 300 IU/kg of unfractionated heparin before aortic cannulation Heparin was neutralised by protamine in a ratio of 1.1 after CPB. Blood samples were



In vitro bleeding time (mean ± SD) *P < 0 05 native vs heparinase +P < 0.05 heparin vs bypass for native and P = 0 15 for heparinase obtained before skin incision, after heparin administration, 10 min after start of CPB, before and after protamine administration *In vitro* bleeding time was assessed by thrombostat (T 4000, VDG, Germany) measured with citrated whole blood without recalcification before and after incubation with heparinase Data were analyzed by ANOVA for repeated measurements followed by Scheffe test. Values as mean ± SD, $P < 0.05$ was considered significant

Results: Heparinase significantly decreased *in vitro* bleeding time in heparinised blood in patients undergoing CPB (figure).

Conclusion: Heparinase reverses adverse effects of heparin on platelets in *vitro*. It seems to be a promising potential alternative to protamine for the reversal of heparin anticoagulation

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A.291 Hydroxyethyl starch slightly impairs measurement of troponin Ic concentrations: an *In vitro* study

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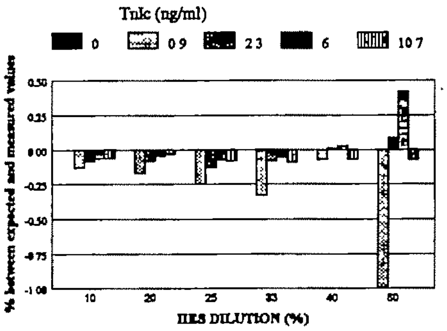
Introduction: Diagnosis of perioperative myocardial infarction is challenging, since there is no gold standard. Troponin Ic (TnIc) have been reported as a sensitive and specific marker of such a complication. However, abnormalities of TnIc measurement have been reported in patients receiving hydroxyethylstarches (HES). The aim of this in-vitro study was to analyze the effects of a step-by-step dilution of serum containing different TnIc levels with HES

Methods: Serum of patients with TnIc values of 0, 0.9, 2.3, 6.0, and 10.7 μg/ml was diluted by 10, 20, 25, 33, 40 and 80% with HES. Immunoenzymofluorometric assay on a Stratus autoanalyser (Dade) was used for the measurement of TnIc For each rate of dilution the ratio between the expected value (EV) and the measured value (MV) of TnIc was calculated.

Results: are reported in the figure.



For serum containing 2.3, 6.0, and 10.7 TnIc ng/ml, the decrease between EV and MV did not exceed 10% at each level of dilution less than 80% However a decrease by 12 to 30% was notified in the serum containing 0.9 ng/ml for all rate of dilution. Large discrepancy of TnIc measurement appeared only at unethical rate of dilution.

Discussion: TnIc determination using Dade assay remains reliable when serum of patients have been diluted with HES in an ethical manner The discrepancy of the measurement observed with 80% HES dilution may be explained by a matricial effect

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A.292 White cell depletion of residual blood after normothermic CPB

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Objective: To validate the report of Gu et al.[1] that leukocyte depletion of residual CPB blood prior to reinfusion significantly improves pulmonary gas exchange in the postoperative period.

Methods: A prospective randomised controlled study of 49 patients undergoing elective normothermic cardiac surgery was undertaken. After weaning from bypass the filter group (F) received residual blood via a leukocyte depleting filter RC400 (Pall). The control group (C) received unfiltered residual blood from the bypass circuit.

Results: The two groups were comparable with respect to pre and operative characteristics. There was no significant difference between groups F versus C in total WBC, neutrophil count, or volume of blood infused (1469 versus 1570 ml). Platelet and Lymphocyte counts were significantly reduced in group F after infusion of residual blood and at 24 hrs postop (Platelets: 154 preinfusion, 144 postinfusion ($p < 0$ 05) and 141 at 24 hours ($p < 0.05$); Lymphocytes 1.9 preinfusion, 1.11 postinfusion ($p < 0.05$) and 1.13 at 24 hrs ($p < 0.05$). The differences in Alveolar-arterial gradient were small and not significant. There were no difference in out-come measures F versus C of extubation time (145 v 178 mins), ICU stay (22 v 23 hrs), or hospital stay (7 5 v 8 days).

Conclusions: In contrast to hypothermic surgery, WBC depletion of residual bypass blood prior to reinfusion does not improve oxygenation after normothermic surgery.

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A.293 Generation of elevated doses of bradykinin in retransfused pleural shed blood during extracorporeal circulation causes acute decrease of peripheral vascular resistance

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Background: The contact of blood with artificial surfaces such as the components of the extracorporeal circulation during cardiopulmonary bypass (CPB) leads to an individual distinct systemic inflammatory response syndrome associated with the release of vasoactive mediators. The severe and acute decrease of arterial blood pressure (AP) specifically after retransfusion of pleural shed blood during cardiopulmonary bypass leads us to evaluate the influence of following pathways proposedly involved: complement activation by terminal complement complex (TCC), granulocyte activation by PMN-elastase, activation of the coagulatiuon system by thrombin-antithrombin III complex (TAT) and bradykinin, a powerful vasoactive mediator activated by kallikrein-kinin system.

Materials and Methods: Patients ($n = 13$, 58 ± 11 years) undergoing coronary artery bypass grafting including the use of the internal mammary artery (IMA). For IMA preparation pleura of the left hemithorax was opened. Blood accumulated within the pleural cavity during clamp-time was sucked into the CPB. With the aortic clamp still in place and with constant flow on the CPB (4 8 ± 0.4 l/min), mean AP and central venous pressure were on line monitored. Systemic blood samples were collected from all patients before retransfusion and after retransfusion immediately after the observed decrease in AP. An additional sample was taken out of the pleural shed blood before retransfusion

Results: Retransfused blood volume from the left hemithorax was 472 ± 258 ml. After 60 ± 15 s AP dropped from 68 ± 15 mmHg to 36 ± 8 mmHg ($p < 0$ 001) Calculated systemic vascular resistance (SVR) dropped from 1124 ± 263 dyn/s/cm^{-5} to 596 ± 153 dyn/s/cm^{-5} ($p < 0$ 001). To compensate the drop all patients had to be treated with bolus application of norepinephrine (2–6 μg) TAT in systemic blood samples increased after retransfusion from 23 2 ± 12 1 to 101 79 ± 44.6 ($p < 0$ 01) while TCC and PMN-elastase showed no significant differences. Bradykinin levels in the pleural shed blood was three times higher (45.4 ± 11 vs 121 2 ± 57, $p < 0.01$) than in both systemic blood samples

Conclusion: The observed drop in SVR after shed blood retransfusion during CPB may be explained by TAT-activation and transfused high bradykinin levels. Intraarterial transfusion of bradykinin in proven dosages mentioned above increases vascular permeability and is a potent vasodilator that acts through B2 kinin receptors to stimulate the release of endothelium-derived nitric oxide, prostacyclin, and hyperpolarizing factor (1). The granulocyte and complement pathways were not found to be activated Although this undesired drop in AP is easily counteracted by single shot injection of norepinephrine, accumulation of shed blood in the pleural cavity should be avoided by continous suction.

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A.294 Trasylol exposure and re-exposure: histamine kinetics in patients undergoing cardiac surgery

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Background: After re-exposure to trasylol (T), adverse reactions have been reported (1) They are commonly associated with a relevant increase of plasma histamine, PH. Therefore we took blood samples for determination of PH in 3 groups of patients (*pts*) undergoing cardiac surgery. pts with first T exposure n = 20, pts with T reexposure (Re-T), n = 18, pts receiving placebo = 0.9% saline solution (P), n = 19.

Materials and Methods: In all pts, anaesthetic manage-ment followed a standard protocol. Dosage of T was applied according to (1) Blood samples for PH determination were obtained, prepared (2) and deep-frozen at predefined time points (see table 1)

Results: Statistically relevant (threefold of pre-value) increased PH levels (1–2 ng/ml) occurred in all groups and at all time points observed in the study, whereas no clinical symptoms of anaphylaxis were reported

Table 1· time points of PH determination and incidence of statistically relevant histamine elevations

Groups	P	T	Re-T
Before test dose	–	0/20	0/18
5 min after test dose	1/19	2/20	1/18
5 min after sternotomy, before begin loading dose	3/19	3/20	2/18
5 min after begin loading dose	–	2/20	1/18
10 min after begin loading dose	1/19	1/20	2/18
20 min after begin loading dose	–	–	4/18

Conclusion: During cardiac surgery, a multitude of histamine liberating stimuli can entail repeated increases in PH concentration in pts with and without T including clinical symptoms (3). In this study, when T or P is administered, the incidence of statistically significant PH increase is about 5–15% in all groups, which is low compared to other phases of surgery. We conclude, that (1) there is no difference concerning histamine liberating potency between groups T, ReT and P; (2) our data suggest that cardiovascular reactions associated with high PH concentrations, especially to T reexposure, are not regularly to be expected; the underlying mechanism of these events may originate from special predisposing immunologic conditions of individual pts

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A.295 Polymorphonuclear neutrophil functions and major oncological surgery

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Introduction: PMN are important cell effectors of immune response. They are directly implied in host defences against micro organisms. Anesthesia and surgery induce complex modifications on PMN's functions some are activated and some are suppressed. This study was designed to observe perioperative PMN's functions after major oncologic surgery.

Methods: Ten cancer patients were studied during twelve days. They were operated for digestive cancer (n = 6) and gynecologic cancer (n = 4). A standardized anesthesia protocol and prophylactic regimen were used for all patients. Different parameters were studied by flow cytometric analysis: complement receptor (CD11b), FcγIII receptor (CD16), phagocytosis capacity, H_2O_2 production without and with stimulating agents (S aureus, PMA, FMLP). Spontaneous migration and chemotaxis were also studied. Blood samples were drawn just before surgery (D0) and at D1, D4, D7, D12 Thirty healthy patients was used as control group. Statistical analysis was made using anova, paired t test and unpaired t test.

Results and Discussion: Five patients developed post operative sepsis. Comparatively with control group, at D0 the patient's PMN were primed (↑CD16, ↑H_2O_2 Spont, ↑H_2O_2 Staph, ↑Phagocytose). Postoperatively this priming was potentiated (↑H_2O_2 Staph, ↑H_2O_2 PMA, ↑H_2O_2 Fmlp, ↑Phagocytose) and the PMN'S were spontaneously activated (↓CD16, ↓H_2O_2 Spont)

Expression of CD16, phagocytosis and production of H_2O_2 are expressed by Mean Fluorescence Intensity (MFI)

MCF	Control (n = 30)	Patients (n = 10)				
		D0	D1	D4	D7	D12
CD16	30	40 17^{+}	13 55*	28.14*	32.42*	34 07*
H_2O_2 (Spont)	3 5	6 03^{+}	17.22	11.24	9.99	11 61
H_2O_2 (Staph)	86	161.8^{+}	352 8*	343 90*	318 50*	329 11*
H_2O_2 (PMA)	240	235 6	498 00*	511 30*	526 00*	497.90*
H_2O_2 (Fmlp)	8.5	11 22	36.11*	33.53*	20 66	24 90*
Phagocytosis	4	6.36^{+}	9 16*	10 22*	9 28*	9 63*

$^{+}$ = $p < 0\ 05$ control versus D0, * = $p < 0\ 05$ D0 vs D1, D4, D7, D12

Conclusion: Perioperatively PMN's functions showed a proinflammatory status This status didn't protect against postoperative sepsis and could paradoxically induce it.

A.296 Effects of midazolam + nitrous oxide + oxygen anaesthesia and surgery on cellular immunofunction in mice

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Goal of Study: The perioperative immune dysfunction can be implicated in development of postoperative septic complication.

We therefore studied the influence of anasthetics alone and combined with surgery on cell mediated immunity in mice

Material and Methods: Twenty BALB/c female mice weighing 20–25 g were ventilated with Ayre T-piece, semi open system, modified for mice 5 animals were anaesthetized with midazolam i.v., 5 animals received N_2O 70% and O_2 30%, 5 animals received both of them, 5 animals served as control without anaesthesia. After 1 hour exposure with anaesthetics the animals were sacrified. An other 20 mice were anaesthetized with midazolam-N_2O-O_2 and operated on (total laparotomy). 5 animals served as control. 15 animals were sacrified after a period of 0.5, 1.0 and 2 0 hours anaesthesia and surgery (5 of each) At the end of anaesthesia arterial blood gas analyses were performed. The thymus, spleen and bone morrow T-lymphocyte subpopulations (CD3, CD4, CD8) were investigated by Fluorescence-Activated Cell Sorter.

Results: The number of helper (CD4) and suppressor (CD8) cells decreased significantly ($p < 0.05$) in thymus supernatant after 1 hour exposure of all anaesthetic combination The surgery and general anaesthesia expressed a highly significant ($p < 0\ 001$) time dependent immunosuppressive effects on CD4 and CD8 cell population in thymus and increasing number of CD3 cells after 0 5 hour In spleen and bone marrow significant changes were not observed in T-lmyphocytes.

Conclusion: The study clearly demontrates the immunosuppressive effects of intravenous and inhalational aneathestetics on T-lymphocyte subsets in mice. The surgery may have an additional unfavorable influence on cellular immunity. In immune compromised patients the post-injury immunosuppression can be responsible for increased number of septic complications.

Attempts have to be made to moderate the obligatory post-injury immunosuppression

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A.297 Influence of cortisol inhibition on the response of IL-6 and IL-10 to surgery

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Background & Goal of the Study: Over the past few years several studies have reported the relationship between interleukins and corticosteroids during surgery. Induction doses of etomidate transiently inhibit enzymes involved in cortisol synthesis. The aim of this study was to analyze if endogenous cortisol modifications cause variations on the response of Interleukins (Il-6 and Il-10) to surgical stress

Material & Methods: The study included 29 patients undergoing elective abdominal surgery randomly divided into two groups. Group 1 (n = 14) received thiopental 4–6 $mg.kg^{-1}$ as anaesthesia inducing agent and group 2 (n = 15) recived etomidate 0 3–0.5 $mg.kg^{-1}$ Blood samples were collected before anesthesia induction (T1), just before incision (T2), 2 hours (T3), 4 hours (T4), 6 hours (T5), 12 hours (T6), 24 hours (T7), and 48 hours (T8) after the induction of anesthesia. Interleukin 6 and 10 were measured in plasma samples by ELISA and cortisol was determinated by radioimmunoassay. Results are expressed as mean ± SD. Statistical comparisons between groups were analysed by MannWhitney test using SPSS for Windows.

Results & Discussion: There were no statistical differences in basal patient data or surgical procedures between the two groups. The release of cortisol was strongly inhibited at T3, T4, and T5, in group 2. IL-6 blood level in group 2 was significantly higher than in group 1 at T5 (194.9 ± 175.6 pg/mL vs 89.45 ± 60.52 pg/mL) IL-10 was higher in thiopental group than in etomidate group at T4 (22 ± 20 pg/mL vs 7.3 ± 4.9 pg/mL)

Conclusions: The differences in IL-6 and IL-10 between both groups suggest that cortisol modulates the release of these cytokines

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A.299 Effects of pure propofol, Diprivan® and Intralipid on active oxygen species produced by activated polymorphonuclear neutrophils

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Background & Goal of Study: Active oxygen species (AOS) produced by activated polymorphonuclear neutrophils (PMN) are involved in tissue injury associated with many acute inflammatory processes. This study was designed to investigate the effects of pure propofol (PPF), a well known antioxidant agent, of its commercial formulation Diprivan® (DI), and of its vehicle solution Intralipid (IL), on AOS produced by activated PMN, using luminol-enhanced chemiluminescence (CL).

Methods: Human PMN were isolated from blood by density gradient centrifugation, counted and suspended in phosphate-buffered saline. Pure PPF dissolved in carbitol, DI and IL were added at various concentrations to PMN batches ($5\ 10^5$ cells) activated by phorbol myristate acetate (PMA) 10^{-6} M, in presence of luminol 10^{-4} M. CL was measured using a Bio-Orbit 1251 Luminometer. Results were expressed as the percentage of inhibition of control value (CL measured in the absence of drug) Linear correlation was fitted by the Pearson's test.

Results: The CL inhibition of activated PMN by DI (PPF in IL) and IL alone was variable, depending on cell batches (table 1). This inhibition was similar for both drugs and not directly related to DI or IL concentrations The CL inhibition by pure PPF was dose-dependent in the range of $5\ 10^{-5}$ to 10^{-3} M and linearly correlated with the log values of the drug concentration ($r = 0.96$; $P < 0.0001$).

Table CL inhibition of 10^{-6} M PMA activated PMN by DI (PPF in IL) at various concentrations, and by IL alone The effects of DI are expressed by the first number in each column and those of IL by the second number in each column

PMN Batches	CL inhibition (%) Diprivan® (μM of PPF)/IL (volume in μl)			
	10/0.09	100/0.9	300/2.7	1000/9
1	0/22	84/73	97/96	98/95
2	0/0	39/35	52/47	53/47
3	25/47	24/19	68/61	71/57
4	–	76/75	70/73	84/82

Discussion: The results of this study showed an unexpected inhibiting effect of IL on PMN CL, interfering with the antioxidant property of pure PPF. When tested in the absence of IL, PPF demonstrated a dose-dependent antioxidant activity against AOS, already observed at clinically relevant concentrations The potential applications of these results in pathologies involving AOS deserve further investigations.

A.300 Cellular mechanisms underlying inhibitory effect of halothane on inducible nitric oxide synthase induction evoked by interleukin-1β

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Background: We have previously reported that halothane (HAL) inhibits interleukin-1β (IL-1β)-stimulated induction of inducible NO synthase (iNOS) in rat aorta[1]. However, the exact site of action of HAL is still unclear. Accordingly, the present study was aimed to elucidate the mechanisms underlying inhibitory effect of HAL on iNOS induction evoked by IL-1β.

Methods: With institutional approval, rings without endothelium from isolated rat thoracic aorta were used.

(1) Effect of HAL on iNOS mRNA expression induced by IL-1β; Rings were exposed for 5 h to (1) IL-1β (20 ng/ml) or to (2) IL-1β+ HAL (3MAC) After exposure, the iNOS mRNA expressions were measured by Northern blot analysis.

(2) Effect of HAL on GTP:cyclohydrolase (GTP.CH) ~ tetrahydrobiopterin (BH4) pathway, GTP CH is a stimulator for induction of BH4 which is an essential cofactor of iNOS activation. Contractile response to phenylephrine (PE, $10^{-9} \sim 10^{-5}$ M) was tested in each ring. After 5 h exposure to (1) IL-1β (20 ng/ml), (2) IL-1β (20 ng/ml) + a GTP:CH inhibitor, 2, 4-diamino-6-hydroxypyrimidine (DAHP, 3×10^{-3} M), (3) IL-1β (20 ng/ml) + DAHP (3×10^{-3} M) + HAL (4 MAC) or (4) IL-1β (20 ng/ml) + HAL (4 MAC), the rings were washed with fresh fluid for 30 min, then a second contractile response to PE ($10^{-9} \sim 10^{-5}$ M) was obtained, followed by the addition of N^G-nitro-L-arginine (LNA 3×10^{-5} M) Contraction was expressed as percentage relative to that induced by first response to PE (10^{-5} M).

Data were expressed as mean ± SEM, and analyzed statistically by ANOVA and unpaired Student's t test. Differences at $p < 0.05$ were considered significant.

Results: IL-1β induced iNOS mRNA expression in rat aorta was not affected significantly by HAL (3MAC). Exposure to IL-1β inhibited the contractile response of rings to PE The addition of LNA (3×10^{-5} M) completely restored the contraction which had been inhibited by IL-1β exposure. HAL (4MAC) reversed IL-1β-induced inhibition significantly. Treatment with DAHP partially reversed the IL-1β-induced inhibition of the contractile response to PE Simultaneous treatment with HAL and DAHP further reversed IL-1β-induced inhibition.

Conclusion: The present study demonstrated, that 1) HAL did not affect IL-1β induced iNOS mRNA expression, 2) DAHP partially reverses IL-1β-induced inhibition, suggesting that the GTP:CH-BH4 pathway plays a role as cofactor for IL-1β-evoked NO production in VSM tissue and 3) HAL further reversed IL-1β-induced hyporeactivity in the presence of inhibition of GTP:CH-BH4 pathway. These findings suggest that the main site of inhibitory action of HAL on iNOS induction evoked by IL-1β lies in the post-transcription process.

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A.301 Leucocyte alterations during hyperthermia

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Background: Leukocyte alterations are determined under several clinical conditions, accompanied with increased body temperatures – e.g during activation of immune system Our aim was to examine the influence of isolated hyperthermia on leukocytes in patients without infections. Therefore we obtained blood from patients with metastatic colorectal carcinoma during induced whole body hyperthermia of 42°C, caused by infrared-A-irradiation. This is used as part of systemic Cancer Multistep Therapy (sCMT), which was started as a phase I/II clinical study

Materials and Methods: Blood samples were obtained before the beginning of the therapy at 37°C (T1), at 40°C (T2), at the end of the plateau of 42°C (T3) and after therapy at 37°C again (T4). Time between investigations was about 2 hours. Examined cells were PMN, lymphocytes and monocytes. In addition, HLA-DR on monocytes as well as L-Selectin on PMN and monocytes were analysed Leukocytes were counted by Cell Dyn 1600® (Abbott), subpopulations and surface markers were investigated by flow-cytometry (FACScan®, Becton Dickinson). Data were compared by using a Wilcoxon rank sum test Significance was defined by $p < 0.05$

Results: Leukocyte subpopulations showed different courses. Percentage of PMN increased significantly under hyperthermia, whereas percentage of lymphocytes and monocytes decreased significantly Absolute cell counts showed similar developments: Number of PMN stayed constant until T3 and increased at T4, whereas number of monocytes and lymphocytes decreased until T3 with a slight tendency back to the starting values at T4. Result was a slight decrease of leukocytes before T3 and a significant increase at T4. HLA-DR and L-Selectin expression on monocytes increased slightly while L-Selectin expression on PMN stayed constant.

Conclusions: Hyperthermia up to 42°C induces significant changes in leukocyte subpopulations. The increase of total leukocytes and PMN-fraction seems to be first (until T3) compensated by substitution of liquids because of the high temperatures At T4 (37°C again), we found increased, but not stimulated granulocytes (constant L-Selectin expression). The decreased number of monocytes seems to be slightly activated, the decreased number of lymphocytes needs to be analysed for changes in subpopulations Further investigations about these results are necessary.

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A.302 Use of single cell gel electrophoresis technique to detect DNA damage in lymphocytes of patients anaesthetized with isoflurane

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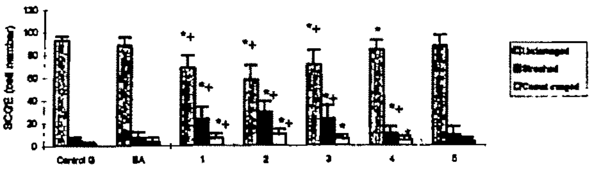
Background & Goal of Study: Although the mutagenic effect of isoflurane is well documented in occupational exposure, its mutagenic effects in patients are not well known[1,2] In this study, the DNA damage were evaluated in lymphocytes of patients exposed to clinical concentrations of isoflurane, using Single Cell Gel Electrophoresis (SCGE) technique.

Material & Methods: ASA I–II 12 adult unpremedicated patients who were undergoing elective surgery and 11 adult control subjects were included in this study. Anaesthesia was induced with thiopentone 6 mg kg^{-1} and fentanyl 1 mg. Vecuronium 0.1 mg kg^{-1} was also given for neuromuscular block. Anaesthesia was maintained with isoflurane 1–1.5% in oxygen Venous blood samples were taken before anaesthesia, at 60. min, 120. min during anaesthesia, postoperative first, third and fifth days. SCGE (Alkaline Comet Assay): Lymphocytes were separated from blood samples and mixed with agarose. Electrophoresis was carried out 40 min at 19 V, 300 mA. Each slide was stained with ethidiumbromide. 100 cells per subject were analyzed under a fluorescent microscope such as undamaged, streched and comet imaged cells. Results were analysed by Student's T, Mann-Whitney U, paired T and Wilcoxon tests

Results & Discussion: A significant increase in the number of streches and comets were observed in the lymphocytes of patients as compared to before anaesthesia and to control at 60. and 120 min during anaesthesia ($p < 0.05$). Increase in DNA damage decreased during postop. period and returned to control and initial values at postop fifth day (figure)



* $p < 0.05$ (with control Group), + $p < 0.05$ (with BA), BA Before Anaesthesia, 1 60 min, 2 120 min, 3 Postop. third day, 5 Postop fifth day

Conclusion: This study supports the existence of an association between reversible DNA damage and anaesthesia with isoflurane by SCGE technique

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A.303 *In vivo* and *in vitro* effects of propofol, midazolam and fentanyl on natural killer cell cytotoxicity

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Background & Goal of Study: The aim of this study was to evaluate in vivo and in vitro effects of propofol, midazolam and fentanyl on natural killer (NK) cell cytotoxicity.

Materials & Methods: After approval from Faculty Ethics Committee and written informed consent from patients; 8 patients scheduled for laparoscopic cholecystectomy, ASA I-II and aged 20–50 years were randomly assigned into two groups (n = 4). In the I. group after the induction with propofol 2 mg/kg and fentanyl 5 μg/kg i.v. anaesthesia was maintained with the infusion of propofol 10–6 mg/kg/h and fentanyl 3 μg/kg/h In the II. group after induction with midazolam 0.2 mg/kg and fentanyl 5 μg/kg i.v. anaesthesia was maintained with the infusion of midazolam 0.15 mg/kg/h and fentanyl 3 μg/kg/h. Peripheral blood samples were collected before induction, 60 minutes after induction and 60 minutes after the end of anaesthesia. In vitro used concentration of drugs were as propofol 10 μg/ml, midazolam 400 ng/ml and fentanyl 10 ng/ml. Radioactive labeled K-562 cells were used as target cells. NK cytotoxicity was calculated with the formula;

% = Cpm (test) – Cpm (med)/Cpm (max) – Cpm (med)

Results and Discussion: Before induction, 60 min. after induction and 60 min. after the end of anaesthesia in vivo NK cytotoxicity of patients anesthetized with propofol and fentanyl were %48.75 ± 14.6, %45 25 ± 13.86, %43.6 ± 13.89 respectively. In vitro values were %47.75 ± 19.19 with propofol, %46 ± 18 45 with fentanyl and %47 ± 16 24 with propofol and fentanyl. In vivo values in the II. group were %63.5 ± 16.8, %58.25 ± 15.56 and %62 ± 20.8 respectively. In vitro values were; %61.25 ± 16.25 with midazolam, %61 25 ± 17 65 with fentanyl and %62 25 ± 16.78 with midazolam and fentanyl There was no significant difference between and in the groups.

Conclusion: When used in clinically relevant concentrations, propofol, midazolam and fentanyl had no supressive effect on NK cell cytotoxicity even in vivo or in vitro.

A.304 Activation of the complement system during autologous blood transfusion: an *in vitro* study with different autotransfusion devices

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Background: A number of autotransfusion devices are commercially available. It has previously been shown that the complement system is activated in shed blood during orthopaedic surgery. The aim of the present study was to determine whether autotransfusion devices lead to complement activation during processing and whether activation initiates throught the classical or the alternative pathway.

Methods: Three different autotransfusion systems were investigated: AT200™ (Hematec, Lund, Sweden), C.A T.S^R (Continuous Autotransfusion System, Fresenius, Germany) and Cell Saver^R (Haemonetics, Braintree, USA) To simulate the degree of complement activation in wound blood, bank blood was activated by CVF (Cobra Venom Factor) in a concentration of 0 2 U/ml during 60 minutes and at 37°C. Activation with CVF was performed in 24 blood bags, eight in each group. After incubation with CVF the blood was processed by the different devices. The experiment was repeated, proceeding exactly as stated above but this time without any CVF activation. The samples were collected from the blood bag, the processed blood and the waste bag. The complement components. SC5b-9 (TCC), C3a and Bb, C4d fragments (Quidel, USA), were determined by an enzyme immune assay (EIA) method.

Results: The concentrations of SC5b-9, C3a and Bb, C4d fragments in processed blood and in the waste bag from C A.T S^R and Cell Saver^R were significantly lower than in the whole blood ($p < 0.01$) in experiments with and without CVF activation Higher concentrations of C3a, SC5b-9 and Bb fragment were found in the study with CVF activation in processed blood from the AT200™ system compared to C.A.T.S^R($p < 0.01$) or Cell Saver^R ($p < 0.01$) The concentration of complement components were decreased in the ultrafiltrate (waste bag) from the AT200™ system compared to the whole blood ($p < 0.05$).

Conclusion: The study shows that the main part of activation occurs in the wound. The activation of the complement cascade goes throught the alternative pathway.

Acknowledgement: We gratefully acknowledge the technical expertise and assistance of Trevor Brett, Quidel, Betchworth, UK.

A.305 Arterial blood gases during shivering and after treatment with meperidine, oxygen or both

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Background & Goal of Study: Postanaesthetic shivering (PAS) causes substantial increase of oxygen consumption with resulting hypoxaemia and metabolic acidosis(1). Meperidine is effective in abolishing PAS(2) This study evaluated whether meperidine could cause hypercarbia and respiratory acidosis when used to treat PAS

Materials & Methods: With IRB approval, forty patients (18 to 65 years old), both sexes, exhibiting shivering in the PACU, were randomly assigned to 4 treatment Groups (n = 10, each): S – saline 3 ml i v., M – meperidine 30 mg i.v., SO – saline 3 ml i.v. plus oxygen 3 L.min^{-1} via nasal catheter, or MO – meperidine 30 mg i.v plus oxygen, as above. Shivering was graded in a four point scale. Room temperature was kept at 26.01 ± 0.8°C. Shivering scores, axillary temperature, heart rate (HR), blood pressure and arterial gases were measured at M0 – during shivering, and at M1 – 15 minutes after treatment. Two-way ANOVA and chi-square were used for between and within groups comparisons.

Results and Discussion: Values are mean ± SD. Meperidine abolished PAS in 100% of patients. At M1, shivering was still present in 70 and 80% of patients in groups S and SO, respectively Blood pressure and respiratory rate did not change at M1 in any group. HR decreased significantly only in Group MO, at M1 Non significant alterations were observed after treatment in axillary temperature (°C) (from 35.8 ± 0.65 to 35.92 ± 0 63, from 36 63 ± 0.59 to 36.18 ± 0 63, from 35 74 ± 0.46 to 35 98 ± 0.43, from 35 41 ± 0.36 to 35 08 ± 0.55), pH (from 7.34 ± 0 04 to 7.4 ± 0 19, from 7.35 ± 0.05 to 7.36 ± 0.06, from 7.34 ± 0.04 to 7.32 ± 0 05, from 7 31 ± 0.07 to 7.31 ± 0.04) or $PaCO^2$ (mmHg) (from 36 63 ± 7.79 to 35.97 ± 8.04, from 30.77 ± 5.77 to 32.08 ± 6 16, from 31.49 ± 4 67 to 34.43 ± 4.56, from 35.07 ± 6.25 to 34.61 ± 8.36), in Groups S, SO, M and MO, respectively Base excess (mEq L^{-1}) did not changed significantly after treatment (from −7.53 ± 3.25 to −6.19 ± 4 23, from −7 77 ± 2.36 to −7 42 ± 2.37, from −7.35 ± 4 23 to −7.37 ± 3 35), in Groups SO, M and MO, but increased significantly in Group S (from −8.88 ± 3.24 to −6.91 ± 3.44). PaO_2 (mmHg) increased significantly in Groups SO and MO at M1 (from 88.05 ± 8.28 to 151.38 ± 31 09 and from 79.77 ± 11.24 to 145 37 ± 26.45) but did not change in Groups S and M (from 79.12 ± 13.72 to 79.41 ± 12.79 and from 87.73 ± 13.34 to 83.71 ± 18.02) SaO_2 (%) also increased significantly in Groups SO and MO (from 94.66 ± 1.53 to 98 ± 0.51 and from 92.55 ± 2.27 to 98 1 ± 0.61) and did not change in Groups S and M (from 91.48 ± 3.89 to 92.46 ± 3.04 and from 93.66 ± 4.33 to 93.69 ± 3.53).

Conclusions: Meperidine (30 mg) abolishes shivering, without causing hypercarbia or affecting axillary temperature, base excess, SaO_2 and PaO_2. Oxygen supplementation must be used as part of the treatment of postanaesthetic shivering

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A.306 Xenon does not trigger malignant hyperthermia in malignant hyperthermia-susceptible pigs

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Background: Since 1951 the inert gas Xenon has been known to have excellent anaesthetic properties. In contrast to Nitrous Oxide no fetotoxicity has been reported (1). The possible triggering of Malignant Hyperthermia (MH) under condition of Xenon anaesthesia has not yet been investigated

Material: After approval by the institutional animal ethics comittee 12 MH-susceptible pigs (Pietrain) were anaesthesid with pentobarbital and buprenorphine. An arterial line (a femoralis), a Swan-Ganz catheter and a venous line (v. femoralis) were placed under these anaesthetic conditions. After a recovery period of 60 min, Xenon anaesthesia (70% inspired) started for 2 hours During that time, heartrate, mean arterial pressure, cardiac output and body temperature were measured every 10 minutes, venous-, mixed-venous-, arterial-blood gases and catecholamines were collected at the same measuring points. After a washout period of 30 min. Halothane exposure started (1% inspired). Within 15 min. an additional bolus of Succinylcholine (3 mg/kg) was adminestered and the investigation was proceeded with the same protocol.

Results: During Xenon anaesthesia no haemodynamic or metabolic changes occurred, indicating the triggering of MH.

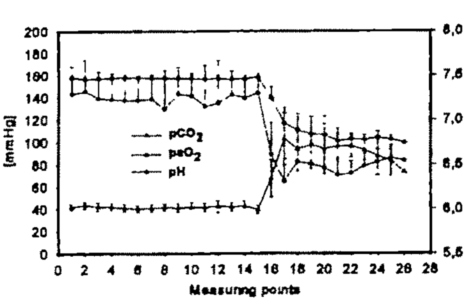

Fig. 1. Arterial Blood Gases, Measuring points 1–13 Xenon anaesthesia, 14–26 Halothane and Succinylcholine

After administration of Halothane and Succinylcholine haemodynamic and metabolic changes, typical for MH, occurred within 10 min. (Fig 1).

Conclusion: Xenon does not trigger MH in MHS-pigs.

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A.307 Central-core-like structures in a family disposed to malignant hyperthermia

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Background and Goal of the Study: Following a fatal MH crisis of a 22 years old man 79 members of his family pedigree were contacted. Until now 31 out of 79 individuals followed our recommendation to undergo an in vitro contracture test (IVCT) 19 of these 31 IVCT tested members also underwent a detailed histomorphological investigation of their skeletal muscle specimens which showed morphological changes similiar to previously described central-core-like structures (CCLS) (1). Goal of the study was to look for a possible correlation between IVCT results and histomorphological changes in the skeletal muscle of the respective family members.

Material and Methods: Between 1980 and 1997 31 members of a MH suspected family were IVCT tested using halothane and caffeine according to the European MH protocol (2) Beginning with the year 1995 in 19 out of 31 individuals also muscle specimens were examined using light and electronmicroscopic methods. This examination was done by an independent investigator unaware of the IVCT diagnoses.

Results and Discussion: Out of the 31 IVCT tested patients 12 (6 female/6 male) had a MHS (MH susceptible), 10 (4 female/6 male) a MHE (MH equivocal) and 9 (8 female/1 male) a MHN (MH negative) diagnosis. 11 out of a total of 19 histomorphologically investigated family members showed CCLS. All 11 CCLS positive individuals were also MH positive in the IVCT (6 MHS: 3 female/3 male, 5 MHE. 3 female/2 male). All 8 CCLS negative probands were tested as MH negative in the IVCT.

Conclusion: 11 members of a MH disposed family revealed striking histomorphological changes described as CCLS. In every case the structures were associated with a MHS or MHE diagnosis and were never seen in a MHN individual of this family. Since so far susceptibility to MH is not believed to be diagnosed by histomorphological changes, a separate morphological entity associated with the occurrence of MH is suggested. Genetic work to confirm this hypothesis is already in progress.

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A.308 Effects of dantrolene on rat fast (extensor digitorum longus) and slow (soleus) skeletal muscles

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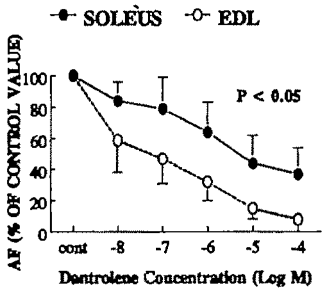
Background and Goal of Study: Dantrolene acts on sarcoplasmic reticulum function of skeletal muscle, inducing a marked negative inotropic effect The aim of this study was to compared the effects of dantrolene on fast (extensor digitorum longus = EDL) and slow (soleus = SOL) muscles in rat

Materials and Methods: The effects of D (10^{-8} to 10^{-4} M) were studied in rat muscle strips from EDL (n = 8) and SOL (n = 8) *in vitro* (Krebs-Henseleit solution, 29 °C, pH 7 40, Ca^{++} 2 5 mM) in the tetanus mode (50 Hz, stimulation frequency 10/min) The active isometric force (AF) was measured. Data are % of control values ± SD. Statistical analysis was performed by repeated-measure analysis of variance and Newman-Keul's test

Results and Discussion: AF was markedly decreased in both groups (maximum decrease in AF 37 ± 17 and 8 ± 4% of control values at 10^{-4} M in SOL and EDL groups respectively), and the negative inotropic effect was significantly greater in EDL group as compared to SOL group (figure).



Conclusion: In our study, dantrolene induced a significant negative inotropic effect both in fast (EDL) and slow (SOL) rat skeletal muscles, with a significant more pronounced effect in fast muscle suggesting a difference in the magnitude of action of dantrolene on these two types of skeletal muscles.

A.309 Secretion of I.v. dantrolene into breast milk after MH therapy

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Introduction: Dantrolene is widely accepted as first line treatment of malignant hyperthermia (MH) crisis (1). Although it has been presumed that dantrolene may cross into breast milk (2), until now no data have been published.

Case Report: We now report the case of a 37 years old woman (62 kg body weight) who developed symptoms of MH (tachycardia, respiratory acidosis, hyperkalaemia, hyperthermia) during general anaesthesia for caesarean section As a developing MH crisis was suspected, a bolus of 160 mg dantrolene was given intravenously and dantrolene therapy was continued over 3 days (560 mg/1 day, 320 mg/2.day, 80 mg/3 day)

Methods: From the 2.–4. postoperative day dantrolene levels in her breast milk were assessed by HPLC-technique (detection limit: 0 02 µg/ml).

Results: Dantrolene was detected in decreasing concentrations (conc.):

Hours after first I v. application	Breastmilk conc (µg/ml)
36 hrs	1 2
43 hrs	0 9
56 hrs	0 55
61 hrs	0 45
66 hrs	0 20
76 5 hrs	0 08
83 5 hrs	0.05

Halflife of dantrolene in the breast milk was estimated by log-linear fitting of the terminal elimination phase. It was calculated to be 9 02 hours

Conclusion: Dantrolene administered intravenously enters breast milk. However, the concentrations found in the patient were unlikely to produce severe side effects in a breastfed newborn. Thus, at least 3 days after dantrolene administration breast milk feeding can be allowed.

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A.310 Perianaesthetic hyperglycaemic and endocrine responses to open cholecystectomy: comparison of general and combined general plus epidural anaesthesia

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Background & Goal of Study: Epidural anaesthesia can attenuate stress responses to surgery$^{(1)}$. Perioperative glucose, ACTH, cortisol and ADH responses were compared between general (G) and combined general plus thoracic epidural (GE) anaesthesia for cholecystectomies.

Materials & Methods: With IRB approval, 24 ASA I or II consenting adults were randomly assigned to Group G (n = 15) and Group GE (n = 9). General anaesthesia included propofol, alfentanyl, isoflurane and vecuronium Group GE received thoracic epidurals up to T4 with 0 5% bupivacaine prior to general anaesthesia. Venous blood was collected for glucose, ACTH, cortisol and ADH measurements at: M0 – baseline, M1 – before skin incision, M2 – after opening of peritoneum, M3 – during dissection of the gall bladder, M4 – during closure of the peritoneum, M5 – before tracheal extubation, and M6 – 20 minutes after recovery. Log-transformed data were treated by two-way, repeated measures ANOVA followed by *post hoc* tests ($\alpha = 0$ 05).

Results & Discussion: Glucose and cortisol increased in Group G from M3 to M6. In Group GE, glucose increased from M2 to M5, but was lower than in Group G at M5 and M6. ACTH did not change in any group. Cortisol did not change in Group GE, and its levels were lower than in Group G at M3, M5 and M6. ADH increased from M2 to M6 in Group G, with no changes in Group GE. (Table I)

Table. Hormonal responses (rounded values, mean ± SD)

	M0	M1	M2	M3
Glucose G	110 ± 40	112 ± 29	110 ± 30	137 ± 36*
GE	94 ± 16	130 ± 24*	131 ± 25*	129 ± 26*
ACTH G	50 ± 27	48 ± 21	57 ± 30	66 ± 29
GE	53 ± 36	55 ± 24	62 ± 37	65 ± 25
Cortisol G	330 ± 191	381 ± 181	740 ± 134	984 ± 960*#
GE	465 ± 136#	399 ± 224	369 ± 223	401 ± 215
ADH G	3 ± 5	2 ± 2	9 ± 11*	21 ± 27*
GE	6 ± 8	3 ± 1	3 ± 18	± 7

	M4	M5	M6
Glucose G	151 ± 41*	153 ± 41*	165 ± 42*
GE	130 ± 32*	120 ± 39*#	107 ± 27#
ACTH G	79 ± 40	72 ± 60	58 ± 39
GE	57 ± 30	48 ± 19	54 ± 25
Cortisol G	1046 ± 739*	1013 ± 539*	1005 ± 483*
GE	505 ± 232	477 ± 182#	543 ± 132#
ADH G	22 ± 20*	10 ± 10*	10 ± 8*
GE	8 ± 8	8 ± 8	7 ± 5

Units Glucose = mg dL^{-1}, ACTH, ADH = pg mL^{-1}, Cortisol = μg mL^{-1} * = $p < 0$ 05 compared to M0, # = $p < 0$ 05 between groups

Conclusion: Combined general plus thoracic epidural anaesthesia attenuates perianaesthetic hyperglycaemic and endocrine stress responses to open cholecystectomy.

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A.311 Metabolic acidosis and respiratory acidosis impair gastroduodenal motility in a pig model

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Background: Acidosis is thought to impair smooth muscle function in various organs (1) However, the effects of acidosis on the gastro-duodenal tract are unknown while its dysfunction has potential perioperative harmful consequences (2) The aim of this study was to evaluate the effects of metabolic (MA) and respiratory acidosis (RA) on upper gut motility A pig model, where gut motility is respected (3), was choisen for this purpose.

Methods: Anesthesia was induced with halothane and maintained with α-chloralose-urethane administration (iv) in 5 intubated-ventilated pigs Increased dead space and perfusion of hydrochloric acid 1 N (150 ml over 30 min) were used to induce RA and MA respectively During these events, measurements of fundic tone using an electronic barostat, antro-pyloro-duodenal phasic motility with perfused manometry and antro-duodenal electric control activity by electromyography were used to evaluate gastro-duodenal function. Statistical significance was determined using ANOVA analysis Results are mean ± SD

Results: The acid infusion decreased pH from 7.41 ± 0 03 to 7.25 ± 0 03 ($P < 0$ 02) without significant change for $PaCO_2$ values (39 7 ± 3 8 mmHg at baseline and 44.4 ± 1.3 mmHg during MA). Respiratory dead space induced a significant decrease in pH (7 25 ± 0.03, $P < 0.02$) and an increase in $PaCO_2$ values (61 2 ± 6.8 mmHg; $P < 0$ 02). Acidosis increased the fundic tone as reflected by a decrease in barostat volumes from 275 ± 83 to 194 ± 88 ml for MA and from 278 ± 93 to 236 ± 106 ml for RA ($P < 0.05$). Pyloric and duodenal basal tones were not affected by both acidosis. A decrease in pyloric contraction amplitude from 95 ± 24 to 62 ± 26 mmHg during MA and from 94 ± 26 to 64 ± 20 mmHg during RA was observed ($P < 0.05$). Decreased arterial pH nearly abolished phase III of the migrating motor complex (MMC) and altered antral control activity that became dysrhythmic

Conclusions: Acidosis mainly affects antral rhythm and has a major effect on fundic tone and MMC. Acidosis may by this way impair gastric emptying and increase intragastric pressure. These data suggest that acidosis may be implicated in perioperative complications such as gastroparesis, emesis and regurgitations of gastric content.

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A.312 Insulin concentrations in samples from stored glucose-insulin-potassium bags

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Background and Goal: Intravenous infusion of soluble insulin added to bags of 10% dextrose containing KCl has been advocated as an effective means of obtaining glycaemic control perioperatively in diabetic patients [1] Although there is little evidence that it achieves better metabolic control [2] it does have the advantage of inherent safety. One major drawback is the need to change the insulin content of the bag if good control of blood glucose is not achieved with the initial infusion, which may lead to delay and inaccuracies in altering infusions One way of avoiding this is to have a number of pre-prepared solutions containing varying amounts of insulin There is evidence that insulin is adsorbed onto PVC [3] Availability of insulin and sterility of these solutions after storage has not been determined

Materials and Methods: 5, 10 or 15 units of soluble human insulin (Eli Lilly) and 10 mmol KCl were added 500 ml bags of 10% glucose (Baxter) in a laminar flow room. 5 bags from each insulin group (n = 15) were stored for 7 days, 5 for 3 days and 5 for 24 hours at 4°C

A 312· Table

Sample time >		1 Hour		3 Hours		5 Hours	
Insulin storage		Mean (SD) insulin conc (mIU ml^{-1})	Mean (SD) % of expected conc	Mean (SD) insulin conc (mIU ml^{-1})	Mean (SD) % of expected con	Mean (SD) insulin conc (mIU ml^{-1})	Mean (SD) % of expected conc
5 Units	7 Days	0 81 (0.04)	8 11 (0 35)	1 71 (0.11)	17 15 (1 13)	2 36 (0 35)	23 63 (3 46)
	3 Days	0 97 (0.36)	9 71 (3 57)	1 81 (0.07)	18 13 (0 74)	2 74 (0 42)	27 41 (4 24)
	1 Day	0 91 (0.34)	9.11 (3 36)	1 65 (0 14)	16.55 (1 39)	3 34 (1 56)	33 42 (15 62)
10 Units	7 Days	2 33 (0 65)	11 63 (3 23)	2 90 (0 46)	14 52 (2 29)	5 60 (0.62)	28 02 (3 08)
	3 Days	2.13 (0 87)	10 64 (4.35)	3 55 (1 60)	17 77 (8 02)	6 79 (2 54)	33 95 (3 65)
	1 Day	1.56 (0 50)	7 78 (2 50)	2 99 (0 52)	14.97 (2 61)	4 45 (0 73)	22 24 (3 65)
15 Units	7 Days	2.83 (1.08)	9.42 (3 62)	8 28 (1 53)*	27 61 (5 09)*	10 25 (3 36)*	34.16 (11 19)*
	3 Days	3 64 (2 11)	12 13 (7 02)	8 99 (4.50)*	29 96 (15 01)*	9 45 (4 99)*	31 51 (16 62)*
	1 Day	5 37 (2 14)*	17 91 (7 14)*	6 38 (2 68)*	21 26 (8 95)*	9 90 (4 44)	33 01 (14 79)

(Student's t test (paired variables, two tailed) demonstrated significant differences ($p < 0$ 05) between 1 and 5 hour samples in all groups and adjacent samples except *).

Samples were taken for immunoenzymetric insulin assay (Medgenix-ins-easia, Biosource Europe) of all bags from the distal end of a PVC giving set attached after removal from storage after 1, 3 and 5 hours in a room at 24°C. Samples at five hours were examined microbiologically.

Results and Discussion: Storage time had little effect on the concentration of insulin found. The amount of insulin in samples increased with time out of cold storage and flow through the giving sets Measured insulin values were between 8 and 18% of the expected concentrations in all bags and 22 and 34% after five hours. There was no bacterial contamination

Conclusion: The insulin content of samples taken from pre-prepared 'glucose-insulin-potassium' bags is not affected by storage time at 4°C. However, availability of insulin from 'GIK' bags is low and varies with time out of cold storage.

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A.313 Parenteral nutrition supplemented with glutamine improves splanchnic blood flow in an endotoxin rat model

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Background and Goal of Study: Recent evidence indicates that enteral and parenteral formulas supplemented with glutamine are beneficial in states with a decreased barrier function of the gut. This barrier function is partial dependent on a sufficient gastrointestinal blood supply. The aim of the study was to determine the effects of parenteral glutamine application on splanchnic blood flow.

Materials and Methods: After placement of a catheter in the jugular vein 32 Sprague Dawley rats received a continuous parenteral nutrition (1054 kJ/kgBw day) for 96 hours. The caloric ratio of carbohydrates.fat:aminoacids was 38:43:19 The animals of group 1 and 2 received a standard aminoacid solution (Aminofusin®) whereas in group 3 and 4 a glutamine supplemented solution (Glamin®) was used Additionally group 2 and 4 received a continuous infusion of endotoxin (E. coli; 1 mg/kgBW day) in the last 24 hours of the experiment. Blood flow to splanchnic organs was measured using radioactive labelled microspheres. Statistics were performed with the Kruskal-Wallis and Whitney-U-test

Results and Discussion: The results (ml/min g) in the table are shown as mean ± SE.

	1 Standard	2 Standard +E	3 glutamine	4 glutamine +E
Small intestine	1.9 + 0.2	1.4 + 0.2*	2.2 + 0.3	1.8 + 0.2+
Large intestine	0.9 + 0.1	0.6 + 0.1*	1.0 + 0.2	0.9 + 0.1+
Liver arterial	0.3 + 0.1	0.4 + 0.1	0.4 + 0.1	0.4 + 0.1
Liver portal	1.6 + 0.2	1.2 + 0.2*	2.0 + 0.3	1.6 + 0.1§,+

*: $p \leq 0.05$ 1 vs 2, §. $p \leq 0.05$ 3 vs. 4; + $p \leq 0.05$ 2 vs 4,

The glutamine enriched parenteral diet improved the splanchnic blood flow compared to a parenteral nutrition with a standard aminoacid solution This effect attenuated the endotoxin induced decrease of blood flow to the intestine.

Conclusion: These data suggest that a glutamine enriched diet may be beneficial in states where the splanchnic microcirculation is diminished and therefore translocation of gut bacteria occurs.

A.314 Preoperative nutritional assessment using the mini-nutritional assessment: a study on 419 elderly surgical patients

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Background and Goal: The MNA has been specifically designed for assessing nutritional status of elderly patients[1]. Awarding to the obtained score, the MNA stratifies patients in: well nourished (24 ≤ MNA < 30) at risk of malnutrition (17 ≤ MNA < 23.5) undernutrition (MNA < 17) It could be useful because malnutrition is a well-known risk factor. Therefore it was prospectively included in the routine preoperative anaesthesiologic evaluation of surgical patients over 60 to describe the nutritional status of this population.

Methods: Every patient over 60 scheduled for elective surgery was submitted to the MNA. It is a clinical score made of 4 additive items· 'anthropometric assessment' based on Body Mass Index (BMI), mid arm and calf circumferences, weight loss, 'global evaluation', 'dietetic assessment', 'subjective assessment', these last 3 items beeing obtained through a specific questionnaire It requires no biological marker.

The MNA forms were filled on site by the anaesthesiologist seeing the patient. Were also recorded. age gender, ASA class, type of operation Results are given as median [extremes].

Results, Discussion: a *Studied patients.* 419 patients (women: 50.4%) were seen between january and october '96. Age. 72 [60–98] yrs, height: 165 [134–186] cm, weight· 68 5 [34–114] kg, BMI· 25 2 [12 8–40.4] kg m^{-2}. Operations were. digestive surg. 62 8%, orthopaedic surg 22.7%, digestive endosc 6.7%, misc 7.9%. score ASA (see table)·

ASA	1	2	3	4	5
n = 419	82	212	115	10	0
%	19 8	50 6	27.4	2 4	0

b. Nutritional assessment (n = 408):

- Median MNA score = 26 [1.5–30]
- Stratification according to MNA score (see table):

MNA score	<17	17–23 5	≥24
n = 408	28	104	276
%	6 9	25 5	67 6

c. Relation MNA/ASA (see table)

	MNA ≥ 24	MNA < 23	
ASA 1–2	218 (75.2%)	72 (24 8%)	n = 290 (100%)
ASA 3–4	60 (50 %)	58 (49 2%)	n = 118 (100%)

$P = 10^{-4} (X^2)$

Conclusion: Tha MNA is well-suited for critical use because it requires no biological marker. Its use showed that about 1/3 of all the examined patients and half of the ASA 3–4 patients were at least at-risk of malnutrition The ASA score alone could not predict poor nutritional status, but its significant relation to the MNA suggests nutritional assessment should be routinely performed in ASA 3–4 patients over 60.

Supported by Nestlé Clinical Nutrition France

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A.315 Is the helium laparoscopy the best approach for pheochromocytoma surgery?

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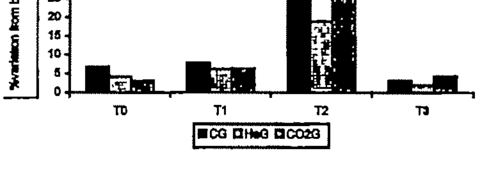
Background: Several studies beings have shown that hipercapnia induced for CO_2-penumoperitoneum produces haemodynamic inestability These physiologic changes could potentially have deleterious effects in patients with pheochromocytoma (FEO).

Aim: This study compares the haemodynamics and plasma catecolamines levels changes (Epinefrine and Norepinefrine) during FEO laparoscopic removal, with helium *versus* CO_2 insufflation for pneumoperitoneum.

Patients and Methods: Twenty patients underwent adrenalectomy were divided in 3 groups according to approach used. He-laparoscopy (HeG, n = 7), CO_2-laparoscopy (CO_2G, n = 7), and open-surgery (CG, n = 6). Variables analyzed were· heart rate (HR), mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), cardiac index (CI), systemic vascular resistance index (SVRI), and pulmonary vascular resistance index (PVRI), increase (% from baseline value) of E and NE plasma levels, arterial blood gases and requirements of vasoactive drugs These measurements were recorded at: T0) baseline, T1) after insufflation or during laparotomy (for CG), T2) during tumor manipulation, T3) after adrenal veins were clamped All data are presented as mean ± SEM. Statistical analysis was performed using analysis of variance (ANOVA) and Bonferroni correction test and χ^2 test.

Epinefrine Changes:



Results: Only at T2, CG showed higher MAP and HR than remain ones ($p < 0.05$) At T2 and T3 CO_2G showed higher MPAP and PVRI E and NE plasma levels are shown in figure. Arterial pH and $PaCO_2$ progressively increased in CO_2G HeG had significant lower requirements of vasoactive drugs at all procedure.

Epinefrine changes are shown in the figure

Conclusions: These results suggest that surgical resection of pheochromocytoma can be safely performed by He-laparoscopic approach.

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A.316 Early diagnosis of postoperative complications after major oncological surgery. Interest of procalcitonin

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Introduction: Post operative complications cause significant morbidity and mortality Successful treatment of these complications needs early diagnosis and appropriate treatment to prevent organ failure. Procalcitonine (PCT) is elevated in patients with sepsis The origin of PCT during systemic inflammation has not been clarified. The aim of this open prospective study was to evaluate PCT and C reactive protein (CRP) as early markers of postoperative complications

Methods: Blood samples were taken perioperatively at D0 (just before surgery) and D1, D2, D3 and D5 (postoperatively) in 15 patients scheduled for major oncologic surgery A standardized anesthesia protocol and prophylactic antibiotic regimen were used for all patients CRP was mesured by nephelemetric technicals (Beckman) and PCT by immunoluminometric technicals (Behring) The patients'postoperative course was classified as complication (infections, septic shock, SIRS, surgical complications) and no complication. Differences between the 2 groups were compared using anova and Student unpaired test

Results: Six patients experienced significant postoperative complications. Comparison between complication group and no complication group showed a statisticaly significant difference at D1 for PCT and at D5 for CRP

	Complication (n = 6)		No complication (n = 9)	
	PCT	CRP	PCT	CRP
D0	0.32	49.2	0.28	38.3
D1	3.80*	114.8	0.89*	93.2
D2	3.23	186	1.72	164.7
D3	3.48	238	1.27	151
D5	1.15	158*	0.67	72*

* $p \leq 0.01$ complication group versus no complication group

Conclusion: These results suggest that PCT in contrast to CRP may be an early marker of postoperative complications in major oncologic surgery patients This preliminary study must be confirmed by subsequent datas.

A.317 Effects of halothane on hormonal secretion of GH3 and AtT-20 clonal cell lines

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Background and Goal of Study: The precise sites and mechanism of action of volatile anaesthetics remain largely unknown Previous work indicated that the volatile anaesthetic, halothane, can alter various stages in the secretion coupling mechanism of cells (1), but the action of clinically relevant concentrations remains obscure. Therefore we have investigated the effects of halothane (1–4%) on two clonal cell lines with well established secretory mechanisms; GH3 rat pituitary cells and AtT-20 mouse tumour cells.

Materials and Methods: Cells at a concentration of 1×10^{-6} in medium (Hams F10 + 10% horse serum + 5% foetal serum) containing known concentrations of agonists were exposed to varying concentrations of halothane in humidified 95% O_2 + 5% CO_2 for two hours. Control samples were exposed to the humidified carrier gas only Supernatant and intracellular samples were assayed for hormonal concentration (RIA and ELISA) and intracellular protein concentration

Results and Discussion: There was no inhibition of prolactin secretion from stimulated GH3 cells when exposed to halothane for two hours. In contrast, ACTH secretion from stimulated AtT-20 cells was significantly inhibited by 4% halothane·

Halothane	ACTH ng/ml		
	0%	4%	
CRF 10^{-8} M	4.4 ± 1.8	2.9 ± 1.3	p < 0.025
Forskolin 0.1 μM	4.7 ± 1.5	3.7 ± 0.3	p < 0.05

Conclusions: Halothane inhibits pituitary hormone secretion dependent on activation of adenyl cyclase/cyclic acid AMP but has no effects on secretion mediated via protein kinase C However both clonal cell lines showed some cell death at 4% halothane.

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A.318 Does isoflurane or nitrous oxide induce micronuclei in human lymphocytes *in vitro*?

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Introduction: Micronuclei (MN) are whole chromosomes or chromosome fragments that are lost during mitosis The induction of MN is a sensitive method for assessing chromosome damage. Since there is an ongoing discussion about the genotoxicity of inhaled anaesthetics, the aim of this study was to assess the potential of Isoflurane or N_2O to induce MN in human lymphocytes in vitro

Methods: With informed consent and approval by the ethics committee, University of Regensburg, lymphocytes were isolated from whole blood of 8 healthy male volunteers and cultured at 37°C for 72 h After 44 h of incubation, cytochalasin B was added to produce binucleated cells (BNC) At the same time exposure to isoflurane or N_2O started Isoflurane concentrations were confirmed by head-space gas-chromatography, concentrations of N_2O by infrared spectroscopy 2000 BNC per sample were scored for the number of MN by immunofluorescent microscopy The mitotic index (BNC/100 Cells) was calculated for evaluating cell proliferation Data were checked for normal distribution and analyzed by ANOVA and paired-sample t-tests

Results:

	MN/500 BNC	Mitotic index
Control	5.0 ± 2.0	20.8 ± 7.8
Isoflurane 0.3 mM	5.0 ± 2.2	18.5 ± 5.8
0.6 mM	5.2 ± 2.8	14.8 ± 6.8*
1.2 mM	5.1 ± 3.1	8.8 ± 2.3*
2.4 mM	na	0.7 ± 0.6*
N_2O/O_2 50%	8.5 ± 1.4*	15.1 ± 6.0*

mean ± SD, * $p < 0.05$ vs Control

Discussion: In vitro isoflurane did not induce MN in concentrations up to 1.2 mM The highest concentration (2.4 mM) could not be evaluated because cell proliferation decreased in a dose-related manner and stopped at 2.4 mM. Cell proliferation is inhibited by volatile anaesthetics (1) The in vitro induction of MN by 50% N_2O/O_2 is in accordance with an increased MN formation in nurses with occupational exposure to N_2O (2). Therefore N_2O is of major concern, when the genotoxicity of a mixed exposure to various inhaled anaesthetics is evaluated

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A.319 Role of dimethyl sulphoxide and methylprednisolone in the prevention of halothane hepatotoxicity

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In this experimental study, we aimed to investigate the effect of dimethyl sulfoxide (DMSO) and methylprednisolone (MP) on the prevention of halothane related hepatotoxicity

The study was performed on thirty male Wistar-albino rats equally divided into 3 groups Enzyme induction was performed by administration of phenobarbital (1 mg/ml) in the drinking water of the rats for 7 days The rats were anaesthetized by 15%02 + 85%N2O + 0.7% halothane (71/min) for 2.5 hours The control group (n = 10) was given only halothane. The DMSO group (n = 10) was given 20% DMSO (4 g/kg) subcutaneously 2.5 hours before anaesthesia. The anaesthesia. The MP group (n = 10) was given MP (30 mg/kg) iintravenously intravenously 2.5 hours before the anaesthesia Thirty minutes after the anaesthesia, rats were sacrificed and liver samples were taken for free radicals and ultrastructural changes. A significant reduction in the value of malondialdehide which was used for determination of free radicals was observed in DMSO (22495.2 ± 3.76 nmol/g) and MP (24475 ± 3.15 nmol/g) groups in comparison to the control group (29952 ± 4.38 nmol/g) ($p < 0.0015$, $p < 0.0032$). Electron microscopic investigation of the control group revealed marked reversible and irreversible changes in the hepatocyte organelles. In DMSO group the hepatocyte organelles showed marked proliferation and in some of these organelles reversible damage was observed. In MP group marked reversible damage was observed in addition to proliferation of the hepatocyte organelles. In experimental studies free radicals were decreased by DMSO catching hidroxyl radicals and MP lipid peroxidation. (1, 2) We found that DMSO and MP decreased liver injury associated with halothane. As the result, in the DMSO and MP groups significant reduction of the free radicals, and observation of less hepatocytic damage in electron microscopy were determined compared to the control group. We regard to these results, we concluded that DMSO and MP are useful chemical substances which can reduce the hepatotoxic effects of halothane.

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A.320

Relationship between the ICG elimination rate (CBIig) and the Child-Pugh score in patients undergoing orthotopic liver transplantation

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Introduction: Indocyanine green clearance (ICG_{CL}) is a global measure of liver function and is widely used as a prognostic parameter of liver disease since it is sensitive to changes in hepatic blood flow and liver cell function (1). However, ICG is not able to distinguish between hepatic arterial and portal venous blood flow and hepatocyte function. But as a dynamic liver function test it may reflect graft function and may be used to predict graft survival and final outcome (2, 3). In addition, the Child-Pugh-Score is widely used classifying liver dysfunction and failure. This classification includes the development of ascites, encephalopathy, decreasing serum albumin and increasing bilirubin levels, as well as a prolonged prothrombin time. According to the deterioration of liver function each variable is given a value between 1 to 3 points. Therefore the aim of this study was to correlate the CBIig as a simple measure of liver function in patients undergoing OLT with the Child-Pugh grade.

Methods: During a 4 months period 23 consecutive patients (7 F, 16 M) undergoing OLT without venovenous bypass in our center were studied. The patients were classified according to the Child-Pugh Score preoperatively. ICG_{CL} was obtained with a double-indicator dilution technique (the COLD™ system, Pulsion, Munich). The indocyanine green decline in blood was detected by a thermistor-tipped fiberoptic catheter in the descending aorta and ICG elimination rate (CBIig) was calculated. For statistical analysis the unpaired T-Test was used.

Results: Among our patients, 6 have been staged as "A" (solely primary hepatoma), 8 as "B" and 9 as "C" (end stage liver cirrhosis due to viral infection and alcoholic genesis). By looking at the relationship between CBIig and the Child-Pugh-Score we found a significant correlation in patients scored Child A ($p < 0.05$). Whereas patients classified Child B and C showed no significant correlation between the CBIig and the Score ($p = 0.4485$).

Conclusion: Although CBIig and Child-Pugh-Score were correlating in Child A classified patients, this correlation was lost in patients with more severe liver dysfunction. Our findings showed that CBIig can not replace the Child-Pugh-Score when liver function is worsening (Child B and C) but both methods are complementary useful.

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A.321

Nitric oxide blood concentrations and haemodynamic changes during liver transplantation

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Background & Goal of Study: Nitric oxide (NO) has been implicated in the hyperdynamic circulation of cirrhotic patients. Following graft reperfusion during liver transplantation (LT) such haemodynamic pattern is even more marked. The study aimed at evaluating if changes in NO blood levels take place during the different phases of LT and if they correlate with the haemodynamic profile.

Material & Methods: The study included seven consecutive LT recipients (6 males, 1 female; mean age 44 years, range 28–54). Jugular blood samples were collected at the following times: (A) before skin incision, (B) at the beginning of the anhepatic phase, (C) 5 min before graft reperfusion and (D) 5 min, (E) 15 min, (F) 60 min, (G) 120 min after reperfusion. NO blood levels were assessed by electron paramagnetic resonance spectroscopy. At the same times, cardiac index (CI) was determined by the thermodilution technique with a Swan-Ganz catheter. Data were analyzed with the ANOVA and the Student-Newman-Keuls tests and correlated with the Pearson test, they are expressed as mean ± SEM.

Results: The profiles of NO levels and CI showed significant differences among times ($p < 0.001$). NO levels at time D (8.1 ± 1.5 arbitrary units) were significantly increased in comparison with levels at times A (5.6 ± 1), B (5.3 ± 1) and C (6.5 ± 1.3) ($p < 0.05$). A further peak in NO levels was found at time F (always occurring after arterial unclamping) (9.6 ± 2) ($p < 0.05$ vs all other times except time D). At time G, NO levels (7.9 ± 1.3) remained significantly higher than times A and B ($p < 0.05$). Regarding CI, it was significantly higher at times D, E, F, G (7.2 ± 0.7, 6.4 ± 0.2, 6.5 ± 0.5, 6.3 ± 0.3 $l/min/m^2$, respectively) in comparison with times A, B, C (4.1 ± 0.3, 3.1 ± 0.4, 3.6 ± 0.2, respectively) ($p < 0.05$). Interestingly, a significant negative correlation was found between NO levels and CI at time D ($p < 0.05$, $r = -0.82$), while a positive correlation was observed at time F ($p = 0.02$, $r = 0.83$).

Conclusions: NO levels increase after graft reperfusion during LT, with two successive peaks occurring after portal and arterial unclamping respectively. The negative correlation existing between NO levels and CI just after graft reperfusion suggests that also other mechanisms are involved in the post-reperfusion syndrome, while NO may be responsible for the success ve persistence of a highly hyperdynamic state.

A.322

Soluble heat shock protein (hsp 60) in plasma of liver transplant recipients. A clinical study

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Background: Heat-shock proteins (hsp) are a family of gene products expressed in response to stress and tissue injury and are known to enhance tissue resistance to ischemia. Their expression has been observed during conditions of diminished oxygen delivery i.e. ischemia and reperfusion in organ transplantation and their role in the immune response of graft rejection is gaining increasing interest. Elevated tissue levels were found in acute rejection after experimental heart transplantation and in kidney biopsies from individuals undergoing episodes of acute and chronic rejection [1, 2] Hence, it was the aim of this study to evaluate the release of hsp 60 into plasma of human orthotopic liver transplant (OLT) recipients in the perioperative period.

Material and Methods: After approval by the IRB we investigated 22 consecutive patients undergoing OLT without veno-venous bypass. Measurements were obtained at baseline (tp 0) immediately after induction of anaesthesia, 5 min. (tp 1), 30 min. (tp 2), 4 and 24 hours (tp 3 and 4) after reperfusion of the graft. Hsp 60 release was assessed by a sandwich Elisa using two monoclonal antibodies specific for human hsp 60. Quantification of released protein was assessed by blotting versus a standard extinction curve of serially diluted recombinant human hsp 60.

Results: Up to 340 ng/ml released hsp 60 were detected in central venous blood of transplant recipients, with most of the subjects showing a maximal release after 5 to 30 minutes of initiation of reperfusion. We found baseline levels of more than 150 ng/ml in two subjects. In all patients who underwent uncomplicated OLT, hsp 60 levels returned to or below baseline levels 24 hours after reperfusion. In a patient with prolonged ICU-stay a remaining high level after 24 hours was detected.

Conclusion: Our study demonstrates the release of hsp 60 into plasma of liver transplant recipients in the perioperative period of OLT. We found a time course of hsp 60 within 24 hours after reperfusion in uncomplicated OLT. An early increase in hsp 60 plasma levels might indicate the influence of organ preservation on cellular response, while the role of this molecule as a predictive value for graft rejection after OLT remains to be determined. Additional work is needed to elucidate the possible protective role of hsp 60 during hypoxia/reperfusion injury in OLT and its role in the immune response.

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A.323 Blood salvage with "cell-saver" *vs* 100 000 dalton filtration

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Background and Goal of Study: During blood salvage, the recovery of blood components is uncomplete as a fraction is lost in the salvage device We hypothesized that a plasmapheresis filter would traumatise the salvaged blood to a smaller extent compared with centrifugation techniques, thereby permitting that a larger fraction of the red cells should be reinfusable

Materials and Methods: In a randomised laboratory investigation two methods of salvage using some degree of saline wash were studied, a conventional "cell-saver" (Group CS) and salvage by filtration using recirculation through a 100. 000 dalton filter (Group F) The content of the original blood to be processed was known as donor whole blood was used, n = 8 in each group. Median values and ranges are given.

Results and Discussion: Red cell recovery was 82 (73–87)% and 81 (74–94)% in Group CS and Group F, respectively The concentration of free haemoglobin in processed blood was 108 (17–160) and 38 (20–64) mg/L in Group CS and Group F, respectively More free plasma haemoglobin was eliminated to the waste bag with the filtration technique, but the haemolysis in processed blood was low, <0 1%, in both groups The recovery of platelets differed significantly between the groups, 10 (5–23) vs 51 (31–63)% during salvage with conventional red cell centrifugation and filtration, respectively. The median recovery of leukocytes was similar, 48 and 60% in Group CS and Group F, respectively About 20% of albumin, total protein and extracellular potassium was recovered when using filtration, whereas the recovery was minimal, <7%, with the cell-saver

Conclusion: Both methods of autotransfusion caused moderate spillage of red blood cells and the levels of free haemoglobin were low in processed blood Filtration gave a larger recovery of platelets, albumin, total protein and potassium as compared with the cell-saver

A.324 Blood saving in dorsal spondylodesis

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Background and Goal of the Study: In a retrospective analysis of 44 patients, operated on dorsal spondylodesis, it proved that they had received a number of mean 3.7 ± SD 2.3 packed cells in the perioperative period In the pilot-study presented here, 36 patients, operated on dorsal spondylodesis, were treated in a protocol with four transfusion-reducing techniques The aim of the study was·

1 Reducing blood loss perioperative 2 Preventing or reducing homologous blood transfusions perioperative.

Materials and Methods: Four transfusion-reducing techniques were combined. I. Preoperative autologous blood donation. Every patient donated 3 × 500 ml blood. 4, 3 and 2 weeks before the operation Iron supplement started 5 weeks before the operation II Preoperative autotransfusion with a cell-saver (Haemonetics Cellsaver V). III Hypervolemic hemodilution After induction of anesthesia, 2 × 500 ml of eloHAES 6% (Fresenius) and 500 ml dextrose-saline was infused IV. Controlled hypotension with isoflurane (Abbott) Only normotensive patients were included in the study

Combining profound hemodilution and controlled hypotension can form a risk for the patient. Oxygen delivery can diminish so that a metabolic acidosis develops Moreover reanimation is difficult with the patient in the fixed knee-elbow posture. Therefore the following safety-measures were taken 1. Only ASA I and ASA II patients were included 2. Controlled hypotension only in normotensive patients and not lower than a M.A.P. of 70 mm Hg 3 Maintaining hypervolemia, aiming at a CVP of 10 mm Hg and a diastolic pulmonary pressure of 15 mm Hg. 4. Ht not below 18% and Hb not below 3 5 mmol/ltr. 5 Continuous measurement of the mixed venous oxygen saturation (SvO2) with a thermodilution fiberoptic pulmonary artery catheter (Opticath, Abbott) The SvO2 reflects the amount of oxygen extracted from hemoglobin. In this way oxygen delivery was monitored

Results: During operation all 36 patients received their 3 units of autologous packed cells and 3 units of fresh frozen plasma. No homologous packed cells, plasma or platelets were given during the operation After the operation 8 patients needed homologous transfusions. a total of 16 units of packed cells and 7 units of fresh frozen plasma 28 patients (= 78%) were operated on without any homologous blood transfusion. During operation the lowest values (mean ± S D) of Hb, Ht and SvO2 were Hb 4 3 ± 0.7 mmol/ltr, Ht 22 ± 3%, SvO2 68 ± 6%

Conclusions: 1 Combined use of four transfusion-reducing techniques resulted in a firm decrease of homologous blood transfusions compared with a retrospective analysis

2 Continuous SvO2 measurement seems a reliable monitor to guarantee sufficient oxygen delivery under the circumstances of controlled hypotension in combination with a low hematocrit

NEUROSCIENCES

A.325 Comparison of spontaneous frontal electromyography, EEG power spectrum and bispectral index for predicting emergence after propofol sedation

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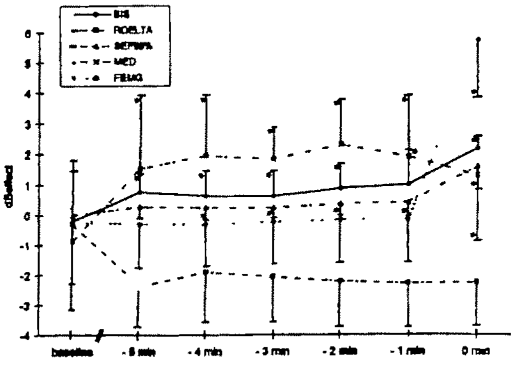
Background: Many electrophysiologic measures have been developed to monitor depth of anaesthesia and to predict emergence (1) The aim of this study was to investigate the accuracy of frontal spontaneous EMG (SEMG), EEG spectral edge 95% (SEF95), EEG median frequency (MF), EEG relative delta power (RDELTA) and Bispectral Index (BIS) to predict emergence after propofol sedation

Methods and Material: After Ethics' Committee approval, 10 informed patients, receiving spinal anaesthesia for lower limb surgery, received a target-controlled infusion of propofol at 4 4 μg/ml for sedation (2) No other drugs were used and patient were aimed at breathing spontaneously via an oxygen face mask. After 36 min the propofol infusion was stopped The different variables were recorded every min before return of consciousness (ROC) and compared with stable baseline values just before stopping the infusion A reliable measure would show a statistically significant change at least 1 min before reaching ROC A decibel transformation with individualized baselines was used to compare variables with different indices on a common scale (3) Statistical analysis was done with ANOVA and if significant two-tailed t-test for paired data was performed.

Results and Discussion: (mean ± SD) Anthropometric data of the patients (2 male, 8 female) were weight 61 ± 9 8 kg, age 40 ± 9 6 years Accuracy of the different measures to predict ROC are plotted in fig 1 As shown, a trend to decrease in RDELTA was found without statistical significance due to large individual variability Relative decrease in slow-wave activity was reflected in increase of MF and SEF95 For MF, clinical interpretation is difficult due to large interpatient variability A monotonic increasing trend during emergence was found in SEF95 and BIS. SEMG increased only statistically at ROC without predictability

Conclusions: After propofol sedation, the BIS and SEF95 are useful to monitor and predict emergence



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A.326 Effects of propofol-sufentanil *vs* midazolam-sufentanil on cortical somatosensory evoked potentials during major spine surgery

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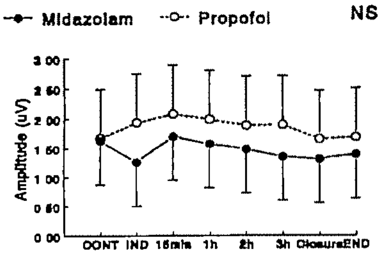
Background and Goal of Study: CSEPs enable neurologic monitoring during spine surgery, but they are depressed by most anaesthetic agents. Nevertheless, the combination of opioids and midazolam is recommended because of moderate effects on CSEPs. Thus, we undertook a prospective study to compare the effects of propofol with those of midazolam during major spine surgery

Patients and Methods: 20 patients were randomly allocated to a propofol (P) or midazolam (M) group. Anaesthesia was induced with either P (3 mg.kg^{-1}) or M (0.3 mg.kg^{-1}), associated with sufentanil (S) (1 μg.kg^{-1}) and vecuronium (0.1 mg kg^{-1}) in both groups; then anaesthesia was maintained with a continuous infusion of either P (10 mg.kg^{-1}h^{-1} for 1 h then 6 mg.kg^{-1}h^{-1}) or M (0.15 mg.kg^{-1}h^{-1}) with in both groups S (0.5 μg kg^{-1}h^{-1}) and oxygen in air (F_iO_2: 60%) We recorded the latencies (P40 and N50) and the amplitude of CSEPs in the awake state (control), and during surgery (induction, 15 min, 1 h, 2 h, 3 h and at the end of the procedure). Statistical analysis was performed by repeated-measure analysis of variance and Newman-Keul's test. Data are mean ± SEM

Results and Discussion: There were no significant differences between groups for age, sexe, duration of surgery and sufentanil doses. We did not observe any significant difference between groups concerning CSEPs latencies (P40, N50) and amplitude (figure). Nevertheless, a significant greater delay of the first voluntary postoperative motor response was observed in the M group as compared to the P group (112 ± 19 vs 44 ± 8 min, $P < 0.05$)



Conclusion: In our study, both anaesthesia regimens allowed a reliable CSEPs monitoring, but M significantly increased the delay of first voluntary postoperative motor response.

A.327 Effects of calculated plasma sufentanil concentration on the haemodynamic and the bispectral index responses to mayfield head holder application

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Introduction: The placement of cranial pins is an acute nociceptive stimulation during intracranial surgery The present study was designed to evaluate the effects of two calculated plasma sufentanil concentrations on the hemodynamic and the Bispectral index (BIS) changes induced by Mayfield head holder (MH) application in neurosurgical patients.

Methods: After Ethics committee approval and informed consent were obtained, 20 ASA I or II patients scheduled for intracranial surgery were studied. Premedication consisted of hydroxyzine, alprazolam and atropine given orally 1 h before surgery. Anesthesia was provided with propofol (PPF) and sufentanil (SUF) using a target-controlled infusion device Patients were randomly assigned to one of two groups according to calculated plasma concentrations: 3 μg ml^{-1} PPF and 0.5 ng ml^{-1} SUF in group I, 3 μg ml^{-1} PPF and 1 ng ml^{-1} SUF in group II. The MH was fixed 33 ± 6.6 min (mean + SD) after induction. Systolic (SAP), diastolic (DAP), mean arterial pressure (MAP), heart rate (HR) and BIS were recorded 1 min before pinning (baseline), 1 min (P1), 2 min (P2) and 3 min (P3) after pinning. Multivariate repeated-measured analyses of variance were applied to the baseline-subtracted measurements of hemodynamic and BIS values. The data were also compared between groups at the different times, using the Student's *t* test $P < 0.05$ was considered statistically significant.

Results: Patients characteristics as well as baseline hemodynamic and Bis values were similar in both groups. Significant overall time effect was observed for all variables but no significant overall SUF effect was detected Increases in SAP, MAP, DAP and HR did not differ significantly between groups. However at P1, the increase in BIS over baseline value was significantly higher in group I (15.0 ± 7.9) than in group II (6.7 ± 6.5).

Mean hemodynamic (mmHg, beats/min) and BIS values at the different times in both groups

Variable	P1		P2		P3		*P* value				
	G1	G2	G1	G2	G1	G2	G1	G2	Time	Drug	Interac
SAP	99.5	104.7	114.8	116.3	111.7	114.0	107.3	108.6	0.002	0.64	0.74
MAP	75.3	75.9	88.9	86.5	83.7	83.1	83.1	80.5	0.008	0.77	0.70
DAP	65.5	63.0	77.4	72.5	71.5	69.6	72.7	68.7	0.016	0.45	0.49
HR	64.9	57.2	71.4	62.7	69.3	61.1	67.0	59.9	0.008	0.17	0.80
BIS	41.4	45.8	56.4	52.1	46.5	46.1	41.6	45.2	0.0001	0.79	0.06

Discussion: Application of the Mayfield head holder was associated with a significant increase in hemodynamic variables whatever the calculated plasma SUF concentration (0.5 or 1 ng ml^{-1}). However, that increase did not exceed 20% of baseline value in both groups In contrast, the increase in BIS observed at pinning was significantly higher in patients with the lowest calculated plasma SUF concentration, suggesting a possible effect of the analgesic level on BIS during nociceptive stimulations.

A.328 The differences in somatosensory evoked potentials changes and neurological deficit according to the location of temporary clips of cerebral arteries

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Background and Goal of Study: Somatosensory Evoked Potentials (SSEP) have been frequently used to monitor cerebral ischemia during cerebral aneurysm surgery. SSEP changes and their relation to postoperative neurologic deficit have been studied many times[1, 2] but the differences according to the location of temporary clips have not yet been evaluated The aim of this study was to evaluate if there are any differences in SSEP changes and neurologic deficit according to the location of temporary clips (middle cerebral artery [MCA], internal carotid artery [ICA] and both anterior cerebral arteries [ACA]) and types of SSEP (median nerve SSEP [M-SSEP] and posterior tibial nerve SSEP [P-SSEP]).

Materials and Methods: We studied 80 patients undergoing anesthesia and cerebral aneurysm surgery. M-SSEP was monitored for MCA and ICA temporary clipping, and P-SSEP for both ACA temporary clipping. SSEP were recorded after induction of anesthesia and dural opening (control value), during temporary clipping, and after relieving temporary clips. A change in cortical amplitude of more than 50%, as compared with control was considered 'significant'. The records were graded as follows: Type I, no change; Type II, insignificant change; Type III, significant change with a complete return to baseline; Type IV, significant change with an incomplete return to baseline. The differences in temporary clip time according to the location of temporary clips, and presence of significant SSEP changes and neurologic deficit were analyzed using one-way ANOVA and unpaired Student's *t*-test

Results and Discussion: Some SSEP changes of MCA clipping reflected neurologic deficit but SSEP changes of ICA or both ACA clipping hardly reflected it.

Type of SSEP	Postoperative Neurologic Examination					
	Normal/Unchanged			Increased Deficit		
	MCA	ICA	ACA	MCA	ICA	ACA
I	18	12	12	1	0	0
II	5	7	7	0	0	1
III	5	7	4	1	0	0
IV	0	0	0	1	0	0

There was no difference in temporary clip time according to the location of temporary clips But temporary clip time was significantly prolonged if there were significant SSEP changes or neurologic deficit.

Conclusion: SSEP can be used to detect significant cerebral ischemia due to MCA clipping. But SSEP monitoring for ICA or both ACA clipping is not so useful in detecting ischemia.

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A.329 Effect of tramadol and fentanyl on somatosensory evoked potentials in sedated volunteers

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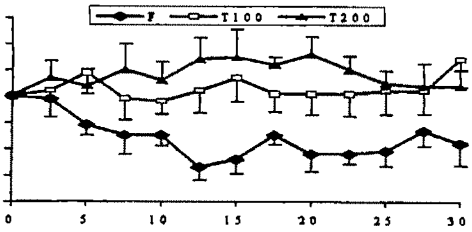
Background and Goal of Study: Tramadol, a centrally acting analgesic, inhibits noradrenaline and serotonin (5-HT) re-uptake, stimulates 5-HT release and has weak opioid μ-receptor activity [1]. Previous data demonstrated that tramadol can cause EEG activation during anaesthesia [2]. Its effect on spinal cord monitoring is unknown. Fentanyl (75 mcg.kg^{-1}), a pure opioid agonist, does not affect somatosensory evoked potentials (SSEP's) [3]. We compared the effect of tramadol and fentanyl on SSEP's during propofol sedation.

Materials and Methods: We studied 8 healthy volunteers aged 20–35 yr. During 3 sessions, each 2 weeks apart, volunteers were sedated with iv propofol to a target plasma concentration using a 'Diprifusor' for a 60 min period. Cortical SSEP's (tibial nerve stimulation) were recorded at 2.5 min intervals throughout each session using C_z-F_z scalp electrodes, and amplitudes A_1 (P1-N1) and A_2 (N1-P2) were measured. At 30 min the study drug [either iv fentanyl 100 mcg (F), tramadol 100 mg (T100) or tramadol 200 mg (T200)] was given over 3 min Venous blood for measurement of plasma propofol concentration was sampled at 30 and 60 min. ANOVA with repeated measures and the paired t-test were used to analyse data.

Results and Discussion: Baseline measurements at steady state sedation for each volunteer were recorded. A_1 decreased significantly after F compared with T100 ($P = 0.029$) and T200 ($P = 0.003$). A_2 showed a similar trend but this was not statistically significant. Plasma propofol concentrations were comparable. The graph shows the percentage change of A_1 from baseline against time (min) following administration of the study drugs



Conclusion: Fentanyl produced a significant decrease in P1-N1 amplitude during sedation with propofol when compared with either dose of tramadol.

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A.330 Effects of propofol infusion on central conduction time during carotid endarterectomy

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Introduction: Cortical somatosensory evoked potentials (CSEP) allow monitoring of cerebral functions and central conduction time (CCT) It is especially used to detect ischemia during neurosurgical procedures. CCT, however, is affected by volatile anesthetics depending upon the concentration used[1]. The effects of propofol on CCT, however, has yet to be studied. We, therefore, recorded CSEP and measured CCT during CEA under TIVA using propofol to determine if there are any changes in CCT corresponding to the doses of propofol used

Methods: Nineteen adult patients aged 67.5 ± 8.4 scheduled to undergo CEA for carotid stenosis participated No premedication was used Anaesthesia was induced with 2 micro gram/kg fentanyl and 1–2 mg/kg propofol after which trachea was intubated following 0.1 mg/kg vecuronium. Anaesthesia was maintained with continuous infusion of propofol, intermittent fentanyl, and oxygen enriched air Mechanical ventilation was kept at ETCO2 at 35–40 mmHg. Blood pressure was maintained at 140–150 mmHg and the body temperature at 34°C or over. CSEP were recorded with transcutaneous electrodes located in the C7-Fz and C'3 (C'4)-Fz elicited by alternate median nerve stimulation. The time between N13 and N20 was regarded as CCT. CCTs were measured before induction, after induction but before the temporary clamping of carotid artery, and during the clamping. During the CCT measurements the rate of propofol was gradually increased from 2 to 10 mg/kg/h then reduced again to 2 mg/kg/h and measurements were made at every 2 mg/kg/h to observe if the changes in CCT depended upon the rate of propofol used. Comparisons were made among the concentrations and with the value of control.

Results and Discussion:

	2	4	6	8	10
Before clamping	6.75	6.78	6.80	6.82	6.86
After induction	6.71	6.79	6.76	6.80	6.83
During clamping	6.81	6.83	6.83	6.83	6.90

That there was no significant differences in CCT between each rates of infusion of propofol in different occasions suggests propofol does not affect CCT in any doses used, or at least not below 10 mg/kg/h. This means propofol allows us to obtain reliable CCT during CSEP monitoring for CEA.

Conclusion: Propofol is useful for CSEP monitoring during CEA as this drug enables us to adjust the rate of infusion as required to get adequate depth of anaesthesia regardless of the CCT measurements for detecting the cerebral ischemia during the surgical procedure

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A.331 Dose-dependent suppression of motor evoked potentials by propofol

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Aim of the Study: Exact knowledge of the influences of anaesthesia on motor evoked potentials (MEP) is required for interpretation of MEP findings during intraoperative monitoring Since it is frequently used for total intravenous anaesthesia (TIVA) in neuroanaesthesia, propofol is of particular interest Therefore, we designed this study to investigate the effect of increasing doses of propofol on MEP.

Methods: Following local ethics committee approval and informed consent ten neurosurgical patients were included in the study. Transcranial magnetic stimulation of the motor cortex was performed with different numbers of pulses (single, double and quadruple) and interstimulus intervals (2, 5 and 10 ms), as well as increasing stimulus intensities (0.6 to 2 tesla). MEP were recorded from three muscle groups of the upper limb Using a target controlled infusion (TCI) pump, propofol infusion was gradually increased up to a target plasma concentration of 6 μg/ml in 1 μg/ml steps MEP were recorded on each target plasma level. Ventilation was assisted by mask as appropriate.

Results: Under stable and reproduceable conditions threshold intensities (single pulse) were established Increasing doses of propofol led to a dose-dependent suppression of MEP amplitudes The amplitudes of the evoked muscle responses were related to stimulus intensity, number of pulses and ISI. Even with supramaximal stimulus intensity (single pulse, threshold + 30%), muscle responses were abolished in 7 of 10 patients at target plasma levels of 2 μg/ml. However, with quadruple pulse stimulation and an ISI of 2 ms, MEP could be recorded in 5 of 10 patients at target plasma concentrations of 3 μg/ml, whereas MEP at the same stimulus intensity were lost with increasing ISI (10 ms).

Discussion: Our investigation shows a dose-dependent suppression of magnetic MEP by propofol. With propofol plasma concentrations of 3 μg/ml required for maintenance of a surgical anaesthetic level[1], reliable intraoperative monitoring of myogenic MEP seems not to be feasible. Even magnetic quadruple pulse stimulation with an ISI of 2 ms, which achieved best results during propofol anaesthesia, did not ensure reliable intraoperative recording of myogenic potentials.

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A.332 The "approximate entropy" as an EEG parameter of anaesthetic depth?

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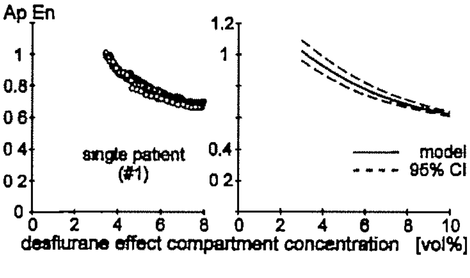
Background and Goal of Study: We hypothesized that the EEG during deep anaesthesia will show more "order" and less "random" than at lower levels of anaesthesia. To quantify regularity we examined the concentration dependence of the approximate entropy[1] (ApEn) in a desflurane mono-anaesthesia during surgery.

Material and Methods: After having obtained institutional approval and informed consent, 12 female patients, age 33–65 yr, who underwent abdominal surgery, were included in the study. After induction of anaesthesia with propofol they received desflurane as the sole anaesthetic agent for maintenance. Between opening and closure of the peritoneum desflurane vapor settings were randomly varied between 0.5 and 1.6 MAC, as long as a clinically adequate depth of anaesthesia was maintained The endtidal concentrations (Capnomac™, Datex) of desflurane were measured. A 3-lead EEG was stored with 125 Hz, the ApEn was computed from 2^{10} data points (= 8.192 s) Median EEG frequency (median) and SEF 95 were calculated, additionally we determined the bispectral index (BIS) (Aspect A-1000). A sigmoid inhibitory E_{max} model was fitted to the concentration-EEG data.

Results and Discussion: The ApEn decreased continuously over the observed concentration range of desflurane (Fig) The Performance of ApEn as an indicator for desflurane concentrations is similar to median, SEF 95 and BIS: We calculated a prediction probability Pk of 0.86 ± 0.06



for ApEn, 0.78 ± 0.06 for median, 0.86 ± 0.06 for SEF 95 and 0.82 ± 0.06 for BIS (mean ± SD), (a value of 1 means indicator predicts anaesthetic concentration perfectly, a value of 0.5 means indicator predicts no better than a 50·50 chance) [2] The low computation time for ApEn allows an on-line analysis.

Conclusions: We believe, that the "approximate entropy" could be an alternative EEG parameter for the on-line analysis of anaesthetic depth.

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A.333 Burst suppression or silent EEG for maximal cerebral metabolic suppression: evidence from flow-metabolism studies

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Background and Goal: Reducing cerebral metabolism may increase the margin of safety in those patients with neurologic injury. This study was designed to investigate whether maximal level of EEG suppression was superior to burst suppression.

Materials and Methods: After obtaining local ethics committee approval and written informed consent, 7 patients (5 F, 2 M, Age 52 5 ± 14 5) undergoing general anaesthesia for resection of acoustic neuromas were recruited. Patients received a standard anaesthetic with routine monitoring (ECG, invasive arterial blood pressure, CVP, pulse oximetry, end-tidal capnography and jugular venous bulb catheter for jugular oximetry – SjO2) At the end of the operation, anaesthesia was maintained with propofol and remifentanil, and the lungs were ventilated in 50% oxygen and air to normocapnia (PaCO2 4 81 ± 0 3 Kpa). Blood pressure was maintained within 15% of baseline with phenylephrine infusions when necessary. EEG activity and burst suppression ratio (BSR) were measured using a bifronto-parietal montage (Aspect A-100, Natick, USA). The middle cerebral artery blood velocity (Vmca) was measured throughout the study with a 2 MHz transcranial Doppler probe (DWL, Sipplingen, Germany) During a period of stable haemodynamics, the EEG activity was varied by adjusting the depth of anaesthesia Vmca and SjO2 were measured at 0%, 50% and 100% BSR and the arterio-venous O2 difference (A-V DO2) was calculated The cerebral metabolic equivalent (CME) was calculated by multiplying the Vmca by the A-V DO2. The results were compared using ANOVA, with a p-value < 0 05 considered significant

Results: The main results are shown in table 1. There were no statistically significant differences in MAP, HR, or PaCO2 at the 3 levels of BSR.

BSR vs CME and % reduction in CME

BSR	0%	50%	100%
CME	254 ± 27	208 ± 20*	160 ± 15*
% reduction CME	0%	17% ± 4**	40% ± 2**

Values are mean ± SE, * p < 0 05, ** p < 0 01

Conclusions: EEG silence is associated with a lower CME than 50% BSR. This may increase the margin of safety in the neurologically injured The effect this has on outcome requires further evaluation

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A.334 A study of adenosine treatment in experimental acute spinal cord injury: effect on arachidonic acid metabolites

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Background and Goal: Vascular mechanisms, production of eicosanoids, free radicals and lipid peroxidation are possible mechanisms of secondary injury after acute spinal cord trauma[1, 2]. In this study the effect of adenosine on arachidonic acid metabolites and lipid peroxidation was investigated in a prospective, randomized, blinded experimental design.

Methods: 37 adult, Wistar-Albino rats were laminectomized and studied in four groups. Group 1 underwent a sham operation. Group 2 received 100 μcg/kg/min IV infusion of adenosine. In group 3 spinal cord trauma was established with the "weight-drop" technique and group 4 received adenosine infusion following trauma. Spinal cord specimens for biochemical and histopathological examination were collected at 30 minutes in all groups. Data were analyzed with Kruskal-Wallis and Mann Whitney U tests.

Results and Discussion: Adenosine infusion after trauma limited the increases in lipid peroxidation but the difference was significant at p = 0.06. The structure of myelin was well preserved in adenosine treated trauma group. However the changes were irreversible in severely damaged areas.

	Group 1	Group 2	Group 3	Group 4
LTC_4 (ng/g)	0 89 ± 0 07	0 46 ± 0 10	1 58 ± 0 09*	1 00 ± 0 10
PGE_2 (ng/g)	2 37 ± 0 30	1 70 ± 0 20	2 30 ± 0 30	4 38 ± 0 40#
MDA (nmol/g)	65 0 ± 7 3	64 4 ± 6 1	78 3 ± 7 8	72 7 ± 7 3

*p < 0.01 compared to group 1, #p < 0 001 compared to other groups

Increased LTC_4 levels increased after trauma indicates the shift of cerebrovasculature response to the vasoconstrictor side. Adenosine infusion following trauma however, Increased PGE_2 levels suggesting that this shift in the balance to the vasodilation side could have beneficial effects on blood flow thus resulting in a possible protective effect in overall.

Conclusion: Following acute spinal cord trauma IV adenosine infusion of 100 μcg/kg/min could attenuate the progression leading to secondary injury but this effect was not effective alone yet.

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A.335 Comparison of sevoflurane and isoflurane on middle cerebral artery blood flow velocity

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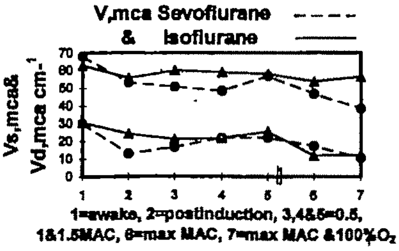
Background and Goal of Study: This study compared the effect of isoflurane and sevoflurane with 70% N_2O in O_2, or 100% O_2, on middle cerebral artery blood flow velocity (V, mca) using the transcranial doppler method. Volatile anaesthetic agents affect cerebral autoregulation. Cho et al[1] demonstrated a decrease in mean V, mca with 1 2 MAC sevoflurane in 100% O_2 which was reversed when N_2O was added.

Materials and Methods: After ethics committee approval, we prospectively randomised 20 ASA grade 1 or 2 patients aged 18–70 yrs to receive either agent. Baseline systolic and diastolic V, mca (Vs, mca, Vd, mca), pulsatility index (PI) and mean arterial pressure (MAP) and heart rate (HR) were measured. After a 20 mg temazepam premed, pre-O_2, and a 1L 0.9% NaCl, thiopentone 4 mg/kg, fentanyl 2 mcg/kg, dropendol 15 mcg/kg and vecuronium 0.1 mg/kg were used to facilitate induction and ventilation via a laryngeal mask airway. Maintenance was with 70% N_2O in O_2 at normocapnia. The volatile was commenced at 0.5 end-tidal MAC and increased by 0 5 MAC increments until MAP fell by 50%. A final measurement was taken at maximum MAC with 100% O_2. Differences between the groups at this endpoint were calculated using the t-test, with significance at p < 0.05.

Results and Discussion: 11 patients received isoflurane and 9 sevoflurane (1 exclusion as a poor doppler trace). Demographic details were comparable and mean trace quality, depth of insonation, HR, MAP and max MAC did not differ between the groups. There was little difference between mean (SD) Vs, mca at maxMAC, but a difference when N_2O was removed and 100% O_2 administered: 38 7 (13.2) v 58 6 (16) cms^{-1} p = 0 032, for sevoflurane and isoflurane respectively.



Conclusion: Our results indicate a similarity in the effects of isoflurane and sevoflurane with N_2O on V, mca The difference at maxMAC in 100% O_2 appears to be a paradoxical effect of sevoflurane on cerebral blood flow resistance in that vasodilatation is occurring under vasoconstricting influences

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A.336 Dynamic cerebral autoregulation during sevoflurane anaesthesia. A comparison with isoflurane

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Background: Inhaled anaesthetics impair the ability to, and the rate of autoregulation in a dose dependant manner. This study examined the effect of 1 5 MAC sevoflurane on dynamic autoregulation.

Methods: After obtaining local ethics committee approval and written informed consent, 16 adults (ASA 1–2, age 54 ± 10 yr, weight 81 ± 11 kg) undergoing non-intracranial neurosurgical procedures were recruited. Patients were allocated to have dynamic cerebral autoregulation (dROR) tested during either sevoflurane or isoflurane anaesthesia With routine monitors in place (ECG, pulse oximetry, end tidal CO_2 and noninvasive blood pressure (Finapress, Ohmeda, U S A), patients received a standardised anaesthetic consisting of propofol 2 5 mg/kg, fentanyl 1 5 μg/kg, and vecuronium 0 1 mg/kg. The lungs were ventilated with 1 5 MAC volatile agent in 100% oxygen to normocapnoea (end tidal CO_2 5 2 ± 0 2 kPa) When necessary, blood pressure was maintained within 20% of baseline levels with an infusion of phenylephrine

Autoregulation Testing: Middle cerebral artery blood velocity (Vmca) was measured using a 2 Mhz transcranial Doppler probe (DWL, Sipplingen, Germany) The probe was fixed in position throughout the study period Vmca and mean arterial blood pressure (MABP) were displayed continuously. Large thigh cuffs were used to evoke a drop in blood pressure Cuffs were inflated to 100 mmHg above systolic pressure for 3 minutes Rapid deflation resulted in approximately 20 mmHg drop in MABP Using an algorithm previously validated, the Vmca response to the drop in MABP was fitted to a series of curves which were used to determine the rate of dROR dROR values were compared using ANOVA P value < 0.05 was considered significant

Results: The main findings of this study are shown In Table 1. There was no significant difference between the two groups in heart rate, MABP, drop in blood pressure, end tidal CO_2 or Vmca The rate of autoregulation awake was within normal limits

Dynamic Rates of Autoregulation

dROR (%/sec)	Sevoflurane	Isoflurane
Awake	29 ± 2	32 ± 2
1 5 MAC	24 ± 2*	4 6 ± 1**

Values are mean ± SE *significantly different from baseline, p < 0 01 **significantly different from baseline and sevoflurane, p < 0 01.

Conclusion: Dynamic autoregulation is better preserved during sevoflurane anaesthesia.

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A.337 Blood flow velocity of middle cerebral artery during mask induction of anaesthesia with high concentrations of sevoflurane in adult patients

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Background & Goal of the Study: It has been shown that high concentration of sevoflurane may be used for induction of anesthesia in adults [1] However, effects of high concentration of sevoflurane on mean blood flow velocity of middle cerebral artery (Vmca) during mask induction of anesthesia remains unknown in adults

Materials & Methods: After approval of the local medical ethics committee and informed consent, 6 ASA 1 adult patients, without cerebral disorder, were included in this study Patients were breathing room air before induction of anesthesia and baseline value of Vmca was then measured using a transtemporal approach (DWL Multidop, Germany) The transcranial doppler probe was maintained at constant position by use of a suitable holder attached to the patient's head. Then, patients were allowed to breath spontaneously high concentration (8 vol%) of sevoflurane in oxygen Heart rate (HR), non invasive mean arterial blood pressure (MAP), inspired and end tidal concentrations of gases were continuously monitored Vmca was then measured continuously during 30 minutes Data are mean ± standard deviation

Results: After introduction of sevoflurane (8 vol%) Vmca rapidly increased reaching a peak value (161 ± 19% of baseline value) at 10 ± 3 minutes During this time, heart rate, mean arterial blood pressure, and end tidal CO_2 ($EtCO_2$) were not significantly modified

Parameters measured at baseline value and ten minutes after 8 vol% of sevoflurane

	Vmca (cm/sec)	$EtCO_2$ (mmHg)	HR (bpm)	MAP (mmHg)
Baseline	41 ± 5	36 ± 4	81 ± 11	103 ± 5
10 min	65 ± 2*	33 ± 7	82 ± 14	102 ± 7

* P < 0 05 vs baseline value

Conclusion: Mask induction of anesthesia using high concentrations of sevoflurane with the spontaneous ventilation technique induced a significant increase of Vmca suggesting a cerebrovascular dilation

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A.338 Effect of desflurane vs isoflurane on intraoperative EEG in elderly patients

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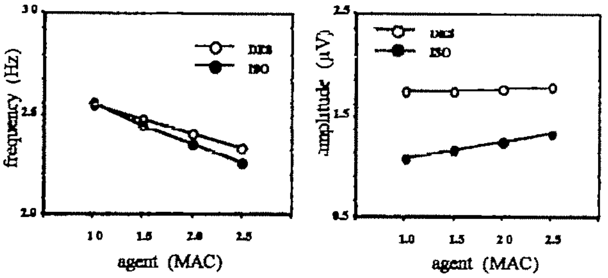
Background: Halogenated inhalation anaesthetics reportedly effect reduction in frequency and increase in amplitude of cortical EEG We wish to present our initial experience on a small number of elderly patients anaesthetised with desflurane, a new potent halogenated agent, in whom intraoperative electrical cortical activity was monitored, as compared to similar patients receiving isoflurane

Methods: During a previously reported Investigation (1) on ASA II and III elderly patients (≥65 years of age), 18 patients (11 receiving desflurane/N_2O and 7 isoflurane/N_2O anaesthesia) were monitored, as a specific operating room clinical practice, with a Datex Cerebral Function Monitor (CFM), in addition to routine monitoring After standard premedication and induction, inspired anaesthetic was titrated to maintaining systemic blood pressure and heart rate within 20% of baseline value End-tidal agent concentration was continuously measured and recorded every 15 min Throughout the procedure (open urological surgery) the CFM measured and plotted every 3 min the average zero-crossing frequency and mean amplitude of cortical EEG. For each patient the CFM tracing, from induction to anaesthesia discontinuation, was divided in 6 equal epochs. The first one was discarded, as expression of initial anaesthetic equilibration, for each subsequent period, the modal EEG frequency and amplitude were taken as representative, and correlated with the correspondent anaesthetic end-tidal concentration (expressed as MAC) Slope and Intercept of 18 individual regressions were averaged, Student's t test was applied to compare regression parameters between the two agents

Results: The two patient groups were comparable in term of demographics, surgical duration and anaesthetic exposure (average MAC) Desflurane induced a MAC proportional decrease of frequency (Hz = 2.699 – 0 149 MAC) and increase of amplitude (μV = 1 691 + 0 038 MAC) on EEG, very similar (figure below) to modifications induced by isoflurane (Hz = 2 716 – 0.183 MAC and μV = 0 911 + 0 165 MAC, respectively) Slope and intercepts for both frequency and amplitude were not statistically different between anaesthetics.



Conclusion: In elderly patients desflurane appears to effect cortical EEG changes (frequency reduction and amplitude increase) very similar to Isoflurane

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A.339 Fast-track supratentorial craniotomies. Experience of 100 patients

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Background & Goal of Study: Prompt recovery is one of the standards of anaesthesia for brain tumours excision It is not that easy for the patient who has received large doses of opioids, Inhalational agents or others At this respect, short-acting both opioids and inhalational agents are very helpful, but still the patients show some residual effects that can interfere with neurological examination

Based on our experience on awake craniotomies (1), we started a program on minimal anaesthesia for the removal of supratentorial brain tumours with the aim of getting some fast-track brain surgery This program included head nerves block, minimal doses of opioids, under-MAC inhalational agents and immediate awakening after surgery

Patients & Methods: In the past two years we have performed a series of 100 fast-track craniotomies for resection of supratentorial gliomas, meningiomas or metastasis Patients were classified as ASA I–II, and aged 18–73 yrs Tumours affecting the cranial base were excluded

Induction of anaesthesia was obtained with propofol 2 mg/kg, fentanyl 1 μg/kg and atracurium 5 mg/kg Afterwards nitrous oxide 50–60% plus isoflurane 0 6% were used. A bolus of propofol 0 04 mg/kg was administered just before head nerves block, and if needed during surgery. To reduce the analgesic requirements, anaesthetic block was performed on those nerves which innervate the scalp and muscular area to be manipulated during surgery, selected among these: frontal (internal + external), zygomaticus-temporalis, temporo-mandibularis, superior auricularis, lower occipital and greater occipital. Each point was anesthetized with only 1–2 cc bupivacaine 0.5% with epinephrine 1:200.000. The incision line was also infiltrated, with a mixture of 10 cc bupivacaine 0.5% with epinephrine 1:200 000 + 10 cc lidocaine 2%. Dura was afterwards anesthetized with cottonoids soaken in lidocaine 2%. After closing the dura inhaled agents were discontinued and a propofol perfusion of 5 mg/kg/h started, and spontaneous ventilation allowed The perfusion was stopped 10 minutes before the end of surgery. The patients were extubated immediately after surgery, neurologically assessed, and transferred to the ICU.

This series of patients was compared with a previous one of traditional anesthesia without head nerve block, with greater doses of opioids, muscle relaxants and inhalational agents, and extubation in the ICU.

Results & Discussion: There were no significant differences between groups in background factors and those related to operation, as duration of surgery. Intraoperative hemodynamic stability was much better in the head nerves block group. Neurological assessment could be quickly and accurately performed in the same operating room or immediately on arrival to the ICU in all patients Patients were discharged from the ICU in 12 to 18 h Their analgesic requirements were also lower They received only one dose of metamizol 8-hrly either iv (2 g) or po (575 mg) The patients could be discharged from the hospital on the 3rd–4th postoperative day

Conclusions: Head trunk nerves block is a useful tool in supratentorial craniotomies to perform fast-track neurosurgery

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A.340 Propofol sedation using a target controlled infusion system in patients undergoing stereotactic pallidotomy

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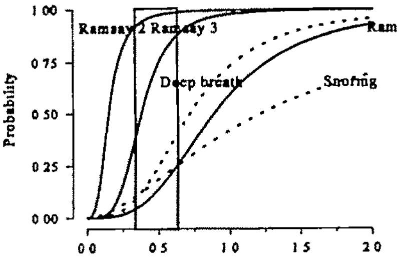
Background and Goal of the Study: Stereotactic pallidotomy is a long lasting surgical procedure where the patient must be awaken, during microstimulation periods. Sedation with propofol allows fast recovery in the precise moment when surgeons need it. Our goal was to estimate the propofol predicted concentration (C_{pred}) ranges that permit adequate sedation to this patients, using a TCI system[1].

Materials and Methods: 3 adult consenting patients were enrolled in the study. All were premedicated with benzodiacepines in the ward Before starting surgery, a target C_{pred} was chosen and the pump started infusing. After allowing for equilibrium between plasma and effect site, sedation score (SS) (Ramsay sedation scale) and the degree of respiratory obstruction (RO) (1: no obstruction, 2: deep breath, 3: snoring, 4: severe obstruction), were measured and recorded At any change in the target level, a new measurement of SS and RO was performed. Logistic regression was used to relate the C_{pred} to the probability of being at (or deeper) level of sedation and respiratory obstruction



Results and Discussion: A total of 71 C_{pred}-effect measurements were done The mean duration of propofol infusion was 365 min. C50 were estimated for all SS and RO levels. The relation between C_{pred} and SS 2, 3 and 4 as well as RO scores 2 and 3, are shown in the graph. The rectangle highlights the levels of C_{pred} associated with adequate sedation without relevant respiratory obstruction.

Conclusion: A target C_{pred} of 0 5 mg/L will keep 75% of patients at sedation score 3 and only 14% at level 4. This concentration is associated with a probability of snoring of 0 12 It can be used as a safe starting point for sedation in this subpopulation of patients

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A.341 Intraoperative complications during pallidotomy for Parkinson's disease. A review of 30 cases

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Background & Goal of Study: Stereotactic pallidotomy is being used as a treatment for medically refractory Parkinson's disease. This neurosurgical intervention is not free of intraoperative complications Although, references on this subject are scarce in the literature.

Our aim has been to point out the frequency and importance of these complications, in order to prevent and treat them promptly.

Material & Method: 30 consecutive patients with Parkinson's disease, who underwent a stereotactic pallidotomy (23 cases) or implantation of a thalamic electrode (7 cases), were studied After the CT scan to localize the target, patients were transported to the operating room and monitored (ECG. pulsioximeter, continuous arterial pressure, $ETCO_2$, urine output) and sedated with propofol (discontinued perfusion) depending on the surgical step. Complications appearing during the procedure were registered. After operation patients overnight in the Postanesthetic recovery room

Results and Discussion: Patients (21 male, 7 female) were sedated with a mean dose of propofol 715 mg (SD.472) during pallidotomy Mean duration time of the procedure was 9.9 hours (SD: 2.6). Intraoperative complications were Mild arterial hypertension, registered in 15 patients, upper airway obstruction appeared in one patient (no tracheal intubation was needed); symptomatic air embolism without hemodynamic changes were noted in 2 patients; arrhythmia (2), anisocoria (1) and seizures (1) were also registered.

Every incident could be treated successfully and intervention could be finished without major complications.

Conclusions: Deep brain recording-guided pallidotomy can be performed with local anesthesia, but the procedures may take a long time, and, in our institution, we prefer to use "conscious sedation". With propofol "discontinuous" infusion the neural noise levels could be detected without interferences. A high rate of minor and potential major complications appeared in our series. Invasive monitoring and promptly detection and treatment of intraoperative complications is mandatory.

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A.342 Brain mapping in assessment of the functional state of the brain

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Background & Goal of Study: Comparison of clinical neurological data to results of the EEG spectral analysis for deriving an integrated exponent of encephalopathy's degree

Materials & Methods: 116 patients with encephalopathies resulting from carbon oxide poisoning (36), postasistolic syndrome (16), brain trauma (30), acute renal failure (7), septic shock (3) and control group (14) were observed. All the patients were admitted in coma (9–21 points according to Glasgow-Pittsburgh Coma Scale).

Electroencephalography (brain mapping) was fulfilled by means of encephalograph "Medicor" in 8 monopolar channels. The estimation of EEG patterns by Zhirmunskaya method [1] was carried out. There were analyzed results of rapid transformation Furie of EEG after rhythmical photostimulation 2, 6, 10, 20 Hz and therapeutical prescriptions. We studied also the figures of absolute and relative power in such diapason: delta (1–4 Hz), theta (5–7 Hz), alpha (8–12 Hz), Beta1 (13–25 Hz), Beta2 (25 Hz and more).

Results: All EEG changes were divided into following types: I-organized (3, 4 groups) (group of control); IV-disorganized with prevalence of alpha-waves (12, 13, 14 groups); V-disorganized with prevalence of delta- and theta activity (16, 17, 18, 19, 20 groups) by Zhirmunskaya classification For quantitative evaluation of EEG-patterns' deterioration we've created coefficient (Delta + Theta + Beta1)/(Alpha + Beta2). Idea of which is based on the fact that Beta2-waves are obligatory component EEG, and Beta1-waves are not typical for the norm [1, 2]. Degree of EEG disorders are presented in table:

Type of EEG	Group of EEG	n	Coefficient	GPS	Degree of EEG disorders
I	3, 4	14	0 96–1.05	35	no disorders
IV	12–15	29	1 6–2 3	29-21	significant
V	17, 18	38	2 5–4.0	18-11	severe
V	19–20	35	4 2–5 5	9-7	extr severe

Is established that coefficient (D + T + B1)/(A + B2) reflects a degree of EEG deterioration, revealed as a result of EEG pattern processing by

Zhirmunskaya method; it was significant degree in 12–15 EEG groups, severe – 17–18, very severe – 19–20. In the EEG groups 3–4 with no EEG disorders coefficient was about 1 (no coma), in patients with extremely severe EEG disorders coefficient varied from 4.1 to 5.5 (coma III).

Conclusion: Coefficient (D + T + B1)/(A + B2) correlates with numerical evaluation of coma depth.

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A.343 Activity of AST in the cerbrospinal fluid in patients with severe brain injury

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Background & Goal of Study: When the cerebral integrity is affected by cerebral trauma, pathological penetration of enzymes into the CSF takes place. This is correlated with degree of neural tissue damage. The aim of the study is to determine the depth of coma according to the CSF enzyme level in cases of cerebral trauma and to undertake prompt and aggressive treatment of these patients.

Material & Methods: The study included 40 patients at the neurosurgical emergency care of the Emergency Centar, Belgrade. AST levels were measured in comatose patients with CT evidence of contusion. On days 1, 3 and 5 after the injury, blood samples were obtained by venepuncture and CSF by lumbal puncture (L4–L5).

Results: AST enzyme activity in the serum five days after the injury remains within the normal values. AST activity in the CSF is highly correlated with GCS on the fifth day after the injury so that it is possible to precisely predict the outcome of treatment and prepare patients for cadaveric transplantation on time (AST 85 U/l, GCS 6).

Conclusions: In severe brain contusion aspartate aminotransferase (AST) was proved to be both clinically and prognostically significant.

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A.344 Thromboelastographic assessment of coagulation during surgery for meningioma

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Changes in haemostasis are often observed in patients undergoing intracranial surgery for meningioma. A concomitant increase in thromboembolic complications and in local fibrinolytic activity have been reported (1). Several mechanisms have been suggested out of which a tumoral release of factors able to alter the haemostatic balance (2). Thromboelastography (TEG) enables a global and dynamic assessment of haemostatic function in whole blood (3). Some TEG variables are analysed: *r* represents the rate of initial fibrin formation, related to the clotting factors and inhibitors, *k* is the clot formation time, mainly affected by the activity of clotting factors and, as well as *alpha angle* and *MA* maximum amplitude, by fibrinogen and platelets. We have measured the potential variations in TEG parameters and usual coagulation tests during meningioma surgery, with or without preoperative embolisation.

Patients and Methods: 22 patients scheduled for meningioma surgery were included. Blood samples were drawn at T0 (before surgery) and at T1 (during surgery after total tumor resection). Blood samples were tested immediately in a computerized TEG Coagulation Analyzer®. Usual clotting tests (PT, APTT, Thrombin time, platelets count, hematocrit, and fibrinogen) were performed at the same time.

Statistical Analysis: a Wilcoxon rank test was used (m ± SD).

Results and Discussion:

Variables (normal range)	Total n = 22		Embolisation n = 9		Non embol. n = 13	
	T0	T1	T0	T1	T0	T1
r (mm) (19–28)	9.3±2.9	9.8±4.4	9.7±2.6	9.4±3.3	9.1±3.2	10±4
k (mm) (8–13)	3.5±1	4.2±2.1	3.7±0.7	4±1	3.4±1.2	4.3±2.7
MA (mm) (48–60)	62.4±6	56.3±9.4*	59.6±5	57.2±6.2	64.3±7.5	55.7±11*
α (°) (29–43)	66.9±5.3	64.6±9.6	64.4±4.4	65.3±5	68.8±5.2	64.0±11

The preoperative profile (T0) of the 22 patients was hypercoagulable, as compared to normal values provided by the manufacturer. At T1 a trend in r and k lengthening and alpha angle decrease were observed while a significant decrease in MA is noted in the non-embolised group, suggesting an impairment in clot strength. No concomitant change in usual coagulation tests was documented.

Conclusion: TEG points out an hypercoagulable state undetected by usual coagulation tests and responsible for the high risk of thromboembolism related to meningioma. Surgery of non-embolised tumor seems to limit this hypercoagulable profile probably through a release in tumoral factors.

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A.346 Effect of hypertonic saline solution on increased intracranial pressure secondary to traumatic brain injury

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Objective: To evaluate the effect of 7.5% NaCl on systemic and brain hemodynamics in acute traumatic brain injury (1, 2).

Materials and Methods: Eleven patients with traumatic brain injury (GCS less than 9), both with and without associated injuries elsewhere, and showing cardiovascular stability. Neurosurgical treatment was not necessary for any patient at that time. A Swan-Ganz catheter was placed in every patient to monitor systemic hemodynamics. Blood pressure, pulse rate and central temperature were continuously recorded. We also registered the hemoglobin level, as well as systemic ventilation and oxygenation. We monitored intracranial pressure (ICP) (intraparenchimal sensor, Camino V4209 monitor) and 02 saturation in the jugular vein (SjvO2) (Opticath Umbilical 4F Abbott).

Every apyretic patient whose ICP was 20 mm Hg or more after being sedated (midazolam and fentanyle), paralyzed (atracurium), slightly hyperventilated depending on their SjvO2, with no hemodynamic disturbance and no less than 10 gr/100 cc hemoglobin received a 1 ml/kg bolus of 7.5% NaCl. The above mentioned variables were measured before, and 5, 30 and 60 minutes after the administration of the hypertonic saline solution.

Statistical analysis: mean ± SD. $p < 0.05$

Results: ICP decreased significantly and cerebral perfusion pressure (CPP) increased significantly as well. The rest of the variables investigated did not change significantly (table).

	Basal	5 min	30 min	60 min
ICP	30.6 ± 7.44	21.2 ± 6.2*	20.7 ± 7.19*	19.8 ± 7.43*
CPP	66.62 ± 5.62	79.13 ± 0.4*	82.2 ± 1.08*	79.97 ± 0.82*
MAP	97.22 ± 13	100.33 ± 6.3	102.9 ± 8.27	99.77 ± 8.25

*p < 0.001

Conclusions: Hypertonic saline solution was effective in decreasing ICP and improving CPP with no change in any other systemic or cerebral hemodynamic variable.

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A.347 Cerebral arteriovenous P_{CO_2} difference as a measure of cerebral ischaemia in severe head injury

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Background and Goal of Study: In head trauma patients, oxygen cerebral metabolism and cerebral blood flow are impaired. During this period, ischemia patterns have been described elsewhere. In clinical practice, cerebral arteriojugular difference of oxygen content ($AjDO_2$) monitoring has been used to detect and prevent cerebral oxygenation imbalance (1). In this patients different index have been used to evaluate cerebral ischemia (2). The aim of this prospective study is to compare the arteriovenous PCO_2 difference ($AVDPCO_2$) with the other index of cerebral oxygen metabolism as a index of cerebral ischemia in patients with severe head injury.

Material & Methods: Sixty severe head trauma patients (GCS < 8), underwent multivariate physiologic studies involving cerebral perfusion pressure (CPP), oxygen jugular saturation (SjO_2), $AjDO_2$, arterio-jugular lactate difference (AVDL), and $AVDPCO_2$, by monitoring jugular bulb oxymetry immediately after their admission in our unit. According to the first determination of $AVDO_2$, patients were separated in three different groups Group I: patients with increased AVDO2 > 8 ml/dl hypoperfusion – ischemia, Group II. patients with $AVDO_2$ = 5–8 ml/dl: normal and Group III: patients with decreased $AVDO_2$ <5 ml/dl: hyperemia. These values were compared (ANOVA for repeated measurements) with the other index of cerebral oxygen metabolism

Results and Discussion: Eleven patients presented ischemic profile, twenty one patients had normal $AVDO_2$ and twenty six presented hyperemia after their admission in SICU. $AVDPCO_2$ was 14.6 ± 9 5, 8.7 ± 2 6 and 5 6 ± 4.1 in groups I, II and III respectively, ($p < 0.05$). AVDL was 1 9 ± 2 5 in Group I, 0.9 ± 1 2 in group II and 3.4 ± 5 in the third group (NS). CPP were 75.6 ± 11 3, 74 7 ± 17 1 and 77 ± 14.1 respectively (NS) and finally CEO_2 in the group I was 53.3 ± 4 7%, 37.8 ± 5 3% and 23.9 ± 8.7% in the group II and III respectively ($p < 0.05$) In the group I, all patients had increased CEO_2 and only 3 patients showed a $AVDO_2$ > 8 after 24 hours, with a wide $AVDPCO_2$, and S_jO_2 < 55%, in spite of the therapeutic maneuvers to improve oxygen cerebral supply. Two out of these 3 patients died (GOS = 1) and one was discharged with moderate disability (GOS = 4) In this study, during the early ischemic phase, $AVDPCO_2$ were greater than normal in group I, and could have been due to a reduction in CBF with oxygen supply dependency (ischemia) and anaerobic CO_2 production.

Conclusions: We can conclude that in head trauma patients, the arteriovenous PCO_2 difference can provide a good method, in the clinical practice, to confirm global cerebral ischemia and that increased CEO_2 may suggest relative cerebral hypoperfusion

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A.348

Correlation of changes in jugular venous oxygen saturation with tissue oxygenation in head-injured patients undergoing hyperventilation therapy

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Background: Monitoring cerebral oxygenation is of great importance in minimising secondary hypoxic and ischaemic brain injury in severely head injured patients. Jugular venous oximetry is the most established method of measuring global cerebral oxygenation and has been particularly useful in monitoring hyperventilation therapy in head injured patients. However, this method of monitoring is not sensitive to regional changes in oxygenation More recently tissue sensors have been used to continuously measure regional tissue oxygenation ($PTiO_2$)[1]. We have compared the changes in jugular bulb oxygen saturation (S_jO_2) and $PTiO_2$ in areas of focal pathology (eg contusion) and outside areas of focal pathology during hyperventilation therapy.

Method: After Local Ethics Committee approval and informed consent, ten patients presenting with severe head injury were studied. A multiparameter sensor (Paratrend 7, Diametrics Medical High Wycombe, UK) was inserted through a specially designed triple lumen bolt into brain tissue Subsequent CT scans confirmed the position of the sensor. A jugular venous catheter was inserted into the right jugular bulb Invasive haemodynamic pressures and ICP were also monitored. Patients were hyperventilated in a stepwise manner by increasing the minute ventilation to decrease the $PaCO_2$ by 0 5 kPa at each step down to a $PaCO_2$ of 3 0 kPa.

Results: Mean CPP, PaO_2 and temperature did not change significantly. Examination of the CT scans revealed the sensor placed inside an area of focal pathology in 4 patients and outside an area of focal pathology in 6 patients. The *change* in S_jO_2 against the *change* in tissue oxygenation showed a good correlation when the sensor was inserted outside an area of focal pathology ($r^2 = 0.68$, $p < 0\,0001$) but no correlation when the sensor was inserted into an area of focal pathology ($r^2 = 0.07$).

Conclusions: (1) S_jO_2 does not always reflect changes in regional oxygenation

(2) Targeted placement of sensors will enable detection of regional changes in brain tissue biochemistry which will not be reflected by jugular bulb oximetry

(3) Measurement of $PTiO_2$ may be a useful adjunct to S_jO_2 in monitoring global cerebral oxygenation

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A.349

CSF *vs* jugular lactates to detect ischaemia during sustained hypocapnia in head injuries. Preliminary results

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Background and Goal of Study: Jugular lactates have been found to be less accurate to detect ischemia during a sustained situation of low cerebral blood flow (CBF) than cerebral spinal fluid (CSF) lactates[1]

Our goal in this study was to compare both jugular and CSF lactates during sustained hyperventilation (HV) in head injuries.

Material and Methods: Eight adult patients with head injury and increased intracranial pressure (ICP) were included and prospective studied. CO_2-reactivity was tested according to previously reported methodology[2]. Within 72 hours after accident patients were hyperventilated for a period of 4 hours During this time pCO_2, jugular (S_jO_2) and arterial oxyhaemoglobin saturation (SaO_2) and ICP were recorded at 30 minutes, 1 hour, 2 hours and 4 hours. Arterial, jugular and CSF lactates were also measured before HV and at 30 minutes and 4 hours after induced hypocapnia Arterio-jugular differences of oxygen ($AVDO_2$) and lactates (AVDL) were then calculated. Results are expressed as mean ± SD or median (min/max) as appropriate.

Results: At the times described pCO_2 values were 35.2 ± 1.8; 31.2 ± 4.6; 27.4 ± 3.9; 26.1 ± 2 5 and 28 2 ± 5 1, and ICP values were 25 (8/68), 7 (1/33), 8 (2/27), 15 (10/44) and 20 (7/43) respectively. According to AVDL no patient developed anaerobic metabolism (AVDL > –0 42 μmol/ml), while CSF lactates were higher than normal values (2 mmol/L[1]) in 3 cases at basal point, 5 cases at 30 minutes of HV and in 7 cases at 4 hours of HV.

Conclusion: CSF lactate values were higher than jugular values during HV. Our results suggest that CSF lactates were more reliable than jugular lactates to detect anaerobic metabolism, although more cases are necessary to confirm this data.

Supported by Grants 96/1783 and 98/1385 from the *Fondo de Investigaciones Sanitarias (FIS).*

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A.350

Hormonal and haemodynamic consequences of moderate hypothermia in head injured patients

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Background: Moderate hypothermia improves neurologic outcome after severe head injury (1). However, mild accidental hypothermia activates parts of the sympathoadrenergical system (2), whereas more pronounced hypothermia depresses it (3). The aim of this randomised controlled investigation was to study the effect of intended moderate hypothermia on the cardiovascular and cortisol response in severe head trauma.

Methods: After IRB approval, 16 patients with severe blunt head injury were either treated with moderate hypothermia (32–33°C, n = 7) or with normothermia (36–37°C, n = 9). Hypothermia was induced within 8 h after trauma and maintained for 48 h Patients were analgosedated at least for three days Heart rate (HR), mean blood pressure (MAP) and plasma cortisol were measured five times during the hypothermia- or corresponding normothermia period and several times after rewarming Norepinephrine (NE) was used to keep cerebral perfusion pressure (CPP) > 65 mm Hg.

Results: Medians of heart rate and mean blood pressure were slightly lower during hypothermia compared to the corresponding normothermia period. Demand of NE for maintaining sufficient CPP was lower in the hypothermia group. Plasma cortisol concentrations did not differ (Tab). During rewarming, heart rate increased to 96 beats/min but blood pressure did not change. Cortisol concentrations increased 4 to 7 days after trauma in most patients of either group. Differences were not statistically significant.

Median HR, MAP, plasma cortisol concentrations and NE infusion in the hypothermia and normothermia group Perc 25%/75% percentile

	32°C	Perc.	37°C	Perc
HR (/min)	67	63/79	96	87/96
MAP (mm Hg)	86	79/90	91	85/91
Corts (nmol/l)	282	256/320	258	178/339
NE (μ/kg/min)	0 16	0 13/0 28	0 31	0 31/0 32

Conclusion: Moderate hypothermia for 48 h after head injury depresses HR and MAP without requiring higher catecholamine dosing. A stress reaction in terms of a cortisol increase was not observed. This findings may indicate that intended moderate hypothermia of 32°C in analgosedated patients neither activates nor depresses the sympathoadrenergic response to the same degree reported during mild or severe hypothermia.

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A.351 Evaluation of carbon dioxide-reactivity and autoregulatory mechanisms in patients with severe head injury

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Background & goal of the study: The status of autoregulatory mechanisms after severe head injury has been a matter of considerable debate Maintaining CPPs above the threshold of 60–70 mmHg should be the main goal in the management of severe head injury, but in patients with impaired autoregulation this could led to an increase in brain volume and ICP. The purpose of this study was to elucidate the status of autoregulatory mechanisms and cerebrovascular CO2 reactivity in patients with severe head injury.

Material & Methods: A prospective study was carried out in 41 patients with severe head injury (Glasgow ≤ 8). Mean arterial blood pressure (MABP), intracranial pressure (ICP), cerebral perfusion pressure (CPP) and oxyhemoglobin saturation (SjO2) were continuously monitored. Cerebral blood flow (CBF) was estimated from AVDO2 and all values corrected for changes in pCO2. CO2 reactivity (CO2R%) was calculated as the percent increase or decrease of estimated CBF per mmHg change in pCO2 To classify autoregulation, we used Enevoldsen criteria (1) for patients in whom ICP changed ≤2 mmHg after increasing MABP. In those patients in whom ICP changed >2 mmHg we used different criteria previously described (2).

Results: Mean age was 30 4 ± 13 (mean ± STD) and GCS was 5.7 ± 1.6. According to corrected basal AVDO2 values, 28 (73.7%) patients were classified as hyperemic (AVDO2 < 1.74 μmol/ml). Cerebrovascular response to CO2 was preserved in all but 2 cases (CO2R% < 1%) In contrast, autoregulation was preserved in 17 (41.4%) and impaired/abolished in 24 (58.5%) At six months, 8 patients died, 1 was in a persistent vegetative state and 9 were severely disabled. Therefore, bad outcome was the final result in 44% of our series.

Conclusions: Although the majority of patients in our study preserved CO2 reactivity, most of them had an impaired/abolished autoregulation during the first 48 hours after injury.

Supported by Grants 96/1783 and 97/0923 from the Fondo de Investigaciones Sanitarias (FISS)

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A.352 Effect of propofol on lipid peroxidation and oedema in experimental brain injury

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Introduction: Preventing and reducing secondary brain injury have bee the focus of recent researches on CNS trauma. Trauma-induced lipid peroxidation is one of the most important factors producing tissue damage in head injury (1). the purpose of this study was to evaluate the antioxidant neuroprotective effects of propofol on cerebral after moderate head injury in rats.

Material and Methods: After approval by the Corporate Animal Welfare Committee of Erciyes University, 24 adult, male, Swiss Albino rats, weighing 200–250 mg were divided randomly to control and propofol groups. Moderate diffuse head injury in rats was performed as described by Mamarou et al (2). A simple head injury device was designed to induce blunt trauma to the protected skull of the rat. A cylindrical column of brass weighing 450 gm was allowed to fall through a 2-m plexiglas tube onto a small rounded stainless-steel disc fixed to the central portion of the skull vault of the rat. The animals were anesthetized by a mixture of ketamine (60 mg/kg) and diazepam (6 mg/kg) injected i p and placed in the prone position n a foam bed with the disc centered immediately under the lower end of the tube of the trauma device Two belts were fastened around the trunk of the rat to prevent it form falling of the foam bed after trauma induction. The weight was allowed to drop freely from the 1-m height through the tube onto the disc The foam bed together with the rat was moved away from underneath the tube immediately after impact to a single hit. A catheter was placed in the right femoral vein for drug administration The propofol group rats received an I.v infusion of propofol (5 mg/kg) for 2 h. and the control group rats received i.v equal volumes of saline solution. Rats were breathing spontaneously throughout the experiment. After 2 h of the experiment, each rat was killed and the brains were rapidly removed. The left and right hemispheres were separated and weighed Malondialdehyde (MDA) was measured by the thiobarbituric acid test and brain water content was determined as the ratio of wet weight to dry weight

Results: The level of total MDA was lower in propofol group than the control group but there was not statistically significant differences between control and propofol groups (p > 0.05). There was no significant differences in brain water content between control and propofol groups (p > 0 05).

	Control	Propofol	p
LP (nmol MDA/g wet wt)	311 ± 39	277 ± 55	1 5
Water (%)	73 ± 8	70 ± 5	1 1

Conclusion: The results of the present study prove that the beneficial effect of propofol in the treatment of traumatic brain injury could be related to decreasing the peroxide lipid products produced as a result of the initial injury. However, further studies should be done in order to determine how long and which doses can be administered to produce significant beneficial effects

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A.353 Oestradiol improves ischaemic neuronal damage in gerbil hippocampus

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Background: The depolarization of the neuronal membrane in cerebral ischemia triggers the release of excitatory neurotransmitters, which is regarded as a crucial factor in the development of neuronal damage Because gonadal hormones influence the metabolism of various neurotransmitters in the mammalian brain, we examined the effects of estradiol and progesterone on the histologic outcome and the anoxic depolarization in ischemia

Methods: Experiment 1 (Histology)· Male Mongolian gerbils weighing 60–80 g were anesthetized with halothane, and the bilateral common carotid arteries were exposed. After the animal was placed in a stereotaxic apparatus in the prone position, estradiol (3, 10, or 30 μg), progesterone (30 μg), or saline (10 μL) was injected intracerebroventricularly. Transient forebrain ischemia was then induced for 3 min by occluding the bilateral common carotid arteries, while the brain and rectal temperatures were maintained at 37.5°C. The histologic outcome was evaluated 7 days after the ischemia by assessing the delayed neuronal death in the hippocampal CA1 pyramidal cells

Experiment 2 (Anoxic depolarization). After the preparation of transient forebrain ischemia, a glass micropipette with a tip diameter of 4 μm was implanted in the right hippocampal CA1 field. The potential shift was monitored between this electrode and the remote electrode. Transient forebrain ischemia was induced and changes in the potential shift were compared among animals pretreated with estradiol (3 μg), progesterone (30 μg), and saline. The data from the two experiments were evaluated by ANOVA with Bonferroni's adjustment.

Results: The number of preserved pyramidal cells was 25 ± 17/mm (mean ± SD, n = 5) in the control group. Estradiol increased the number of preserved neurons, the effect being significant at a dose of 30 μg (171 ± 70/mm, p < 0.01). Progesterone did not affect the histologic outcome. The forebrain ischemia produced a sudden and acute shift in the potential at an onset latency of 54 ± 11 s in the control group with a maximum amplitude of 22 ± 3 mV. Neither estrogen nor progesterone affected the anoxic depolarization.

Conclusion: The pretreatment of estradiol mitigates the ischemic neuronal damage without affecting the anoxic depolarization

A.354 Potassium channel blockers blunt hypoxic cerebral vasodilatation in the awake dog

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Background: During hypoxia, the cerebral blood flow (CBF) increase may be mediated by activation of ATP sensitive potassium (K+) channels (1). The present study investigated the effect of glibenclamide and glipizide, on CBF during acute hypoxia in the awake dog

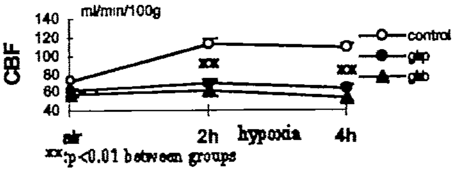
Methods: Sixteen Beagle dogs (mean weight 12 ± 2 kg) were studied. On the study day, the dogs were studied awake during three periods: in normoxia and after 2 and 4 h normocapnic hypoxia in a 45 m3 atmosphere controlled chamber (FIO2 = 10%, FICO2 = 3.5%, FIN2 = 86.5%) During both first stages, the animals were randomly allocated to receive glibenclamide (glib) 10 mg/kg (n = 6), glipizide (glip) 10 mg/kg (n = 6) or placebo Thirty minutes later, after hemodynamic measurements and arterial blood withdrawal for blood gases, glycemia and K+ measurements, radiolabelled microspheres (Ce^{141}, Ru^{103} ou Sc^{46}) were injected into a left atrial catheter for regional CBF measurements The brain was totally dissected in 38 samples.

Results: Mean PaO2 decreased from 84 ± 2 mmHg in air to 44 ± 2 mmHg in hypoxia without differences between groups. Biological results are shown in the table

		Air		Hypoxia	
		baseline	treatment	2 h	4 h
	control	4.4 ± 0.1	4.0 ± 0.1	3.9 ± 0.1	4.3 ± 0.2
K+	glib	4.0 ± 0.1	3.6 ± 0.1*	3.4 ± 0.1**	3.3 ± 0.1**°
	glip	4.1 ± 0.1	3.7 ± 0.1*	3.6 ± 0.1**	3.8 ± 0.1
	control	5.3 ± 0.1	7.6 ± 0.6*	6.9 ± 0.6	5.4 ± 0.1
Gly	glib	5.2 ± 0.2	7.3 ± 0.5**	4.2 ± 0.5	3.4 ± 0.3**°
	glip	5.5 ± 0.1	7.4 ± 0.5**	5.5 ± 0.4	3.8 ± 0.3**

Gly: glycemia (mmol/l) K+ potassium (mmol/l), * $p < 0.05$, ** $p < 0.01$ vs baseline, ° $p < 0.01$ vs control group

In the control group, CBF increased by 53% after 2 h and 46% after 4 h hypoxia This increase was blunted after glib and glip (figure) Regional CBF followed the same patterns in all areas



Conclusion: There were moderate glycemia changes induced by sulfonylureas, but hypoglycemia is known to enhance CBF (2). These results suggest that potassium channel activation plays a key role in cerebral regulation

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A.355 Imipramine chronic treatment up-regulates 5-HT_{1A} receptor in rat hippocampus membranes

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5-hydroxytriptamine receptor subtype 1A (5-HT_{1A}) in the rat hippocampus appears to be implicated in the psychopharmacological effects of the antidepressant imipramine (1). Our aim was to determine the possible changes in 5-HT_{1A} receptor characteristic in rat hippocampus in response to both acute and chronic imipramine administrations.

Materials and Methods: 28 male wistar rats were injected with saline or imipramine (10.9 mg/kg i.p.) acutely (three times/day × 1 day) and chronically (one time/day × 20 days). 5-HT_{1A} receptors were characterised with (^3H)-8-OH-DPAT saturation experiment according to the methods of Pazos et al (2) in membranes from hippocampus. Binding data were analysed using Ligand software Results were analysed by ANOVA test followed by Bonferroni post-test

Results: The affinity of (^3H)-8-OH-DPAT for 5-HT_{1A} receptors were in a similar range in all studied groups. Acute treatment with imipramine did not modified 5-HT_{1A} receptor density. Chronic treatment with imipramine significantly increased (38.18%) ($P < 0.01$) the density of 5-HT_{1A} receptors (427 ± 50 fmol/mg of protein and 309 ± 22 fmol/mg of protein, imipramine and control, respectively)

Conclusion: Chronic treatment with imipramine up regulated 5-HT_{1A} receptors in rat hippocampus membranes. This event could be related with its analgesic effect in chronic pain.

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A.356 Low extracellular Ca^{++}/Mg^{++} ratio opposes anaesthetic actions on old hippocampal neurones

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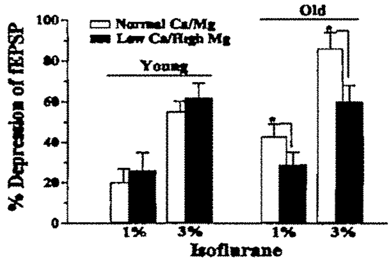
Background and Goal of Study: Preliminary studies showed that ageing enhances anaesthetic-induced depression of the evoked dendritic field excitatory postsynaptic potentials (fEPSP) without any effect on the presynaptic volley in hippocampal slices[1] We hypothesized that a presumed ageing-induced increase in $[Ca^{2+}]_i$ may lead to the observed enhanced vulnerability of old hippocampal neurones to isoflurane actions To investigate this assumption, we recorded evoked fEPSPs in young and old hippocampal slices during perfusion with normal perfusate and low Ca^{2+}/high Mg^{2+} medium. The latter manoeuvre is known to reduce $[Ca^{2+}]_i$.

Materials and Methods: Hippocampal slices (400 μm thick) were prepared from Old (~24 months) and young (~3 months) Fisher 344 rats. fEPSP were evoked by stimulation of stratum radiatum and were recorded extracellularly at the dendritic field of the CA1 neurones. In a submerged recording chamber, slices were randomly incubated and perfused at 35°C with normal perfusate containing 2 mM Ca^{2+} and 2 mM Mg^{2+} or low Ca^{2+} (1 mM)/high Mg^{2+} (3 mM) medium before application of isoflurane.

Results and Discussion: In normal perfusate, the magnitude of isoflurane suppression of fEPSPs was greater in slices taken from old rats compared to those taken from young rats During perfusion with low Ca^{2+} high Mg^{2+} medium, subsequent application of isoflurane depressed the fEPSPs in young slices to the same extent as in aged slices (cf Figure; * indicates $p < 0.05$, Mann-Whitney U-test)



Conclusion: We conclude that decreasing $[Ca^{2+}]_o$ reverses the ageing-induced potentiation of isoflurane actions Therefore, the increased sensitivity of excitatory synapses of aged hippocampal neurones to anaesthetic actions might be due to a sustained rise of $[Ca^{2+}]_i$ associated with ageing

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A.357 Markers of neuronal injury during liver transplantation: a preliminary report

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Background and Goal of study: Neurological complications contribute significantly to morbidity and mortality associated with liver transplantation [1]. S100 and neuron-specific enolase (NSE) are proteins which indicate neuronal injury after ischaemic stroke, intracerebral haemorrhage, minor head injury [2] and cardiopulmonary bypass [3] The serum concentrations of these proteins correlate with outcome We investigated these markers in 5 patients during liver transplantation.

Materials and Methods: With Local Ethics Committee approval, 5 patients (ASA IV–V, age 30–65) scheduled for liver transplantation were recruited. All patients received a standardised general anaesthetic. Blood samples were taken post-induction (A), at the beginning (B) and end (C) of the anhepatic phase, and at skin closure (D). The samples were immediately centrifuged and the plasma frozen at −60°C. Plasma concentrations of S100 and NSE were analysed using an immunoluminometric assay. Neurological status, liver and renal function were assessed preoperatively and postoperatively

Results and Discussion: Results are shown in Table 1. There was no significant change in NSE levels S100 levels increased significantly during liver transplantation.

Table 1

Patient	A	B	C	D
1	0 09	0 28	0 36	0 96
2	0 17	0 31	0 58	0 73
3	0 21	0 37	1 25	0 46
4*	6 15	3 19	4 16	2 75
5	0 22	0 94	0 67	0 64

S100 levels in mcg/l *Patient in hepatic encephalopathy

Conclusions: Plasma concentrations of S100 increase during liver transplantation The values are markedly elevated in encephalopathy The use of S100 as a marker of neuronal injury during liver transplantation warrants further investigation

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LOCAL AND REGIONAL ANAESTHESIA

A.358 Lignocaine + clonidine *vs* lignocaine + bupivacaine: comparison in peribulbar anaesthesia

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Introduction: The purpose of this study was to compare the effects of clonidine or bupivacaine on akinesia and haemodynamic status during peribulbar anaesthesia for cataract surgery

Methods: After informed consent and institutional approval, 100 patients, scheduled for ophtalmic surgery, were included. A two injection sites technique was used by the same experimenter followed by mechanical orbital compression for 10 min. The anaesthetic mixture was administered at constant speed with a pump (12 ml/min), at room temperature, without adjustment of pH. The patients were randomly divided into two groups which received 6 ml lidocaine 2% + 6 ml bypivacaine 0 5% in group **B** (n = 50), 11.5 ml lidocaine 1% + 75 g clonidine in group C (n = 50), each + 250 UI hyaluronidase Efficacy of the block was assessed 10 min after injection (ie after compression) by an independent observer, according to the degree of residual movement akinesia of extraocular muscle was scored good for less than 2 mm eye movement vertically or horizontally, akinesia of orbicular muscles was scored good for complete akinesia or slight movement in either or both eyelid margins. The need for reinjection or not was left to the surgeon to decide Arterial pressure, heart rate and capillary oxygen saturation were measured non invasively before the block, after injection and every 10 min during surgery The two groups (Gaussian distribution) were compared using chi-square test and Student t test A P value < 0.05 was considered significant.

Results: Groups B and C were comparable for the variables of sex, age, weight and axial length of the eye No significant difference was found concerning extraocular and orbicular muscle akinesia (Fig. 1) After preoperative reinjection of 6 to 8 ml when necessary all the operations took place under satisfactory condition In all cases analgesia was satisfying. The haemodynamic profiles measured were similar between the two groups but 7 patients in group B vs 0 in group C presented an episode of hypertension above 200 mmHg systolic value, requiring specific treatment No SpO2 lower than 94% was found

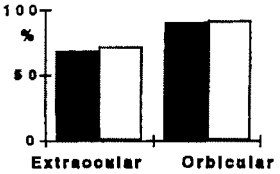

Fig 1 percentage of good akinesia

Conclusion: This randomized study shows that adding clonidine to lidocaine 1% is a good alternative to bupivacaine An equivalent quality motor block is obtained, combined with better haemodynamic stability.

A.359 Effect of volume and speed of injection of local anaesthetics on akinesia during peribulbar block

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Introduction: The purpose of this study was to evaluate the effect of the volume and the speed of administration of local anaesthetics on akinesia after peribulbar anaesthesia for ophthalmic surgery

Methods: After informed consent and institutional approval, 100 patients (ASA I, II, III), scheduled for cataract surgery, were included in this study A two injection sites technique was used by the same experimenter followed by mechanical orbital compression for 10 min A mixture of 50% bupivacaine 0.5%, 50% lidocaine 2% and 250 UI hyaluronidase was administered at room temperature, via low compliance tubing, with a pump (Becton Dickinson). The patients were randomly divided into 4 groups (n = 25): group *A* received 3 ml at the upper site and 6 ml at the lower site at a speed of 5 ml min^{-1}; group *B* received the same volumes at a speed of 12 ml min^{-1}, group *C* received 4.5 ml at the upper site and 9 ml at the lower site at a speed of 5 ml min^{-1}; group *D* received the same volume as group C at a speed of 12 ml min^{-1} Efficacy of the block was assessed 10 min after injection (ie after compression) by an independent observer, according to the degree of residual movement akinesia of extraocular muscle was scored good for less than 2 mm eye movement vertically or horizontally, akinesia of orbicular muscle was scored good for complete akinesia or slight movement in either or both eyelid margins. Additionally, injection pain was assessed by questioning the patients and scored from 0 to 3 according to whether it was negligible (0), low (1), moderate (2), or required to stop the injection (3) The four groups (Gaussian distribution) were compared using chi-square test and ANOVA method. A *P* value < 0 05 was considered significant

Results: The 4 groups were comparable for the variables of sex, age, weight and axial length of the eye Concerning extraocular muscles a significant difference was found between group D, and groups A, B, C No statistical difference was noted concerning the pain scores obtained in each group. No patient suffered such pain that the protocole had to be discontinued No side effect was noted during the observation period

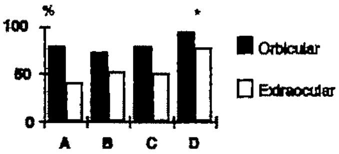

Figure 1 percentage of good akinesia

Conclusion: The quality of akinesia after peribulbar anaesthesia depends on both the volume and the speed of administration of local anesthetics. The best results are obtained with a large volume (13 5 ml) and the higher speed of administration (12 ml/min). These are well tolerated

A.360 Sub-Tenon's *vs* retrobulbar anaesthesia for cataract surgery

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Background and goal of the study: The effectiveness and safety of the sub-Tenon's anesthesia in ocular surgery has been described (1, 2) In this study sub-Tenon's and retrobulbar anesthesia for cataract surgery in outpatients are compared.

Materials and Methods: Sixty patients undergoing cataract surgery on both eyes, within six months of each other, were divided into two random groups. One group of thirty patients received sub-Tenon's anesthesia for the first procedure and retrobulbar for the second. The other group received first retrobulbar anesthesia and sub-Tenon's for the second procedure.

The local anesthetic consisted of a 4 ml injection of a 1·1 mixture with lidocaine 2%, bupivacaine 0 5% and hyaluronidase without epinephrine. After injection ocular pressure was applied for 20 min No premedication, van Lint block or i v. sedation were used.

Twenty minutes after the injection the anesthetist and the surgeon evaluated independently the effectiveness of the anesthesia Patients' satisfaction with the anesthesia and operation was evaluated by using a standard oral questionnaire

Results and discussion: There was no statistical difference between the groups in respect to age, sex, and time between the two operations. Both techniques had similar anesthetic properties There were no anesthetic or surgical complications recorded

In the patients' view the retrobulbar injection caused more pain and discomfort in comparison with the sub-Tenon's injection. After the patients had experienced both of the anesthetic techniques 36 out of 60 preferred sub-Tenon's and only 11 retrobulbar anaesthesia

Conclusions: Sub-Tenon's anesthesia technique is safe and effective for patients undergoing cataract surgery It has proved to be significant less painful procedure compared to retrobulbar anesthesia. The questionnaires confirm that patients feel more comfortable with sub-Tenon's anesthesia

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A.361 Haematoma frequency in peribulbar anaesthesia

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Introduction: The patient population coming for intraocular surgery commonly uses aspirin to inhibit platelet aggregation or nonsteroidal anti-inflammatory drugs (NSAID) or needs warfarin for anticoagulation Retrobulbar high pressure haematoma postpones the planned eye operation and may cause compression of the circulation and ocular nerve and lead to permanent blindness of the eye. Because of this it is important to avoid peribulbar haematomas as far as possible. Patients are advised not to take warfarin for two days and aspirin for three days before surgery. Anyhow, many patients disobey these orders.

Methods: 1150 consecutive patients coming for eye surgery requiring peribulbar block, were interviewed about their use of aspirin, NSAID and warfarin. Diabetes mellitus, use of systemic cortisone and doctors estimate for the relation between orbita and bulbus (1–3) was registered. The appearance and the size of the possible haematoma was evaluated as. 1 = spot haematoma, 2 = half or less around the eye, 3 = all round the eye, but no pressure, 4 = retrobulbar haematoma with pressure Fisher exact test was used to evaluate the significance of the results.

Results: Warfarin was used by 6.1%, aspirin by 35.7% and NSAID by 20.2% of the patients Warfarin, aspirin and NSAIDs did not predispose to haematomas The frequency of haematomas was 4.1% and 55.3% of these were minor spot haematomas. No high-pressure retrobulbar haematomas were induced. There were no statistical difference between staff anaesthesiologists and doctors in training in the haematoma frequency (3 7% vs. 5.6%). 33.8% of the patients reported to have haematoma tendency, but this did not affect the incidence. The anatomical distance between orbita and bulbus, diabetes mellitus or cortisone-treatment did not increase haematoma frequency.

Conclusion: In the practice of our department there is no indication to limit the patients use of aspirin or NSAIDs. It is recommended to make sure that the warfarin anticoagulation is not over the therapeutic level.

A.362 A retrospective review of 7235 consecutive regional anaesthetics for cataract surgery

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Background & Goal of Study: The basic goals for successful anaesthesia in ophthalmic surgery include anaesthesia of the eye, akinesia of the external eye muscles, and low intraocular pressure. Use of regional and local anaesthesia for cataract surgery provide excellent anaesthesia and operating conditions, and may be safe in elderly outpatients, who frequently exhibit several coexisting diseases We report a retrospective study of 7235 consecutive regional anaesthetics for cataract surgery performed between September 1995 and September 1997

Material & Methods: In the last two years 7235 patients underwent ambulatory elective cataract extraction and intraocular lens implantation. All blocks were performed using local anaesthetic mixture (0.75% bupivacaine and 2% lidocaine with 1:100.000 adrenaline) and 150 IU hyaluronidase. The total volume of the local anaesthetic was 10 ml. For peribulbar anaesthesia, modified technique described by Fry and Henderson was used, and the depth of the injection was 20–25 mm, avoiding the muscle cone For retrobulbar block, 4 ml was injected into the muscle cone through the inferolateral lower lid entry. Local anaesthesia was too performed with topic application of lidocaine. In all patients, a mechanical orbital compression device (pressure, 40 mmHg) was then applied for 15 minutes to reduce intraocular pressure.

Results: Peribulbar anaesthesia was performed in 40.1% of patients, retrobulbar block in 54.9% and topic anaesthesia in 4.8%. As complication of our casuistic, we registered in 19 patients retrobulbar haemorrhages (in 5 cases surgery was suspended), in three patients occurred globe perforation (two of them with retrobulbar needle); acute pulmonary oedema was found in 2 patients (they were admitted in intensive care unit). The oculocardiac reflex was found in six patients. In 3 cases we had apnea following retrobulbar block, and one patient presented intraoperative seizures, with the need of tracheal intubation The mean time of observation in the recovery room was 120 minutes, and thereafter all patients could be discharged.

Conclusions: Satisfactory akinesia and analgesia for cataract surgery can be produced using regional block, with fewer serious complications and it is relatively easy to perform for anaesthesiologists well experienced with regional methods.

A.363 Prevention of hypotension after spinal anaesthesia for elderly patients: a comparison of intravascular administration of crystalloid, colloids and no prehydration

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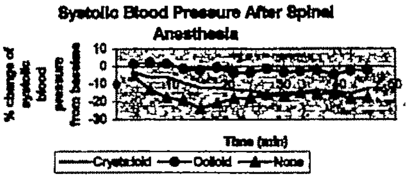
Background and Goal of Study: Hypotension after spinal anesthesia for elderly patients remains a common and potentially serious complication. A growing number of clinical studies have shown that there was no realistic policy in preventing spinal anaesthesia-induced hypotension although prehydration may reduce the incidence of hypotension (1, 2) The present study aimed to investigate the influence of volume loading with crystalloids, colloids versus no prehydration on the spinal anaesthesia-induced haemodynamic changes in patients undergoing orthopaedic surgery

Materials and Methods: The study was conducted on 45 patients (mean age 54, ASA I–II) after local ethic committee approval was obtained In the supine position a baseline systolic blood pressure (SBP), heart rate (HR) and central venous pressure (CVP) were recorded. Patients randomly allocated into 3 groups. Group 1 (n = 15) received 500 cc normal saline 0.9%, group 2 (n = 15) received 500 cc 6% hydroxyethyl starch over a 10 minute-period before the spinal anaesthetics. Group 3 (n = 15) received no significant prehydration. Spinal anaesthesia was performed in the lateral decubitus position at the L_3–L_4 interspace with a 22G needle using 3 ml of bupivacaine 0.5%. All the patients were given a crystalloid infusion at 100–150 ml/h during the surgery. SBP, HR and CVP were measured at 3-minute intervals for 45 minutes. When SBP decreased to less than 75% of the baseline value, 3 mg of ephedrine was administered.



Results and Discussion: After spinal anaesthesia, the average of SBP decreased 11% in crystalloid group, 2% in colloid group and 16% in nonprehydrated group ($p < 0.001$). The patients requiring ephedrine 20% in group 2, 29% in group 1, 66% in group 3. Incidence and frequency of ephedrine use and mean doses were lower in the group 1 and group 2 than group 3 ($p < 0.05$). CVP decreased 2% in group 1, 7% in group 3 and increased 3% in group 2 ($p < 0.001$). There was no difference between group 1 and group 2 ($p > 0.05$), but group 3 was significantly lower than the other groups ($p < 0.05$) HR values were similar.

Conclusion: We concluded that prehydration with crystalloid or colloid are warranted for spinal anaesthesia-induced hypotension.

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A.364 Cardiovascular effects of crystalloid and colloid solutions during spinal anaesthesia

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The ideal fluid regimes for patients scheduled for spinal anesthesia is discussed controversial. Particular in elderly, multimorbid patients the advantages and disadvantages of crystalloid and colloid solutions have to be weighed carefully. Also the cardiovascular effects during spinal anesthesia are researched in healthy young volunteers or in animals The present study was designed to comparatively analyze crystalloid and colloid fluid regimes in terms of hemodynamic responses by using invasive hemodynamic monitoring

Methods: After institutional ethic committee approval and informed consent 24 ASA II–IV patients undergoing hip surgery following trauma were enrolled for the study Hemodynamics were recorded with a pulmonary artery catheter, an ECG and an arterial line. Group A received 500 mL hetastarch 6% and group B 1500 mL lactated Ringer's solution Following fluid administration spinal anesthesia was conducted with 3 mL bupivacaine 0.5%. Hemodynamics were recorded prior to fluid administration, before spinal puncture and 10, 20 and 30 min following spinal puncture Hypotension was defined as a decrease of mean arterial pressure to less than 70% of baseline value Intraoperative blood loss was measured exactly. Statistical analysis were performed by paired and unpaired Student t-test and by ANOVA for repeated measures with Bonferroni correction A p < 0 05 was considered significant.

Results: We found no significant differences in demographic datas, analgesia level and intraoperative blood loss between the study groups. We observed hypotension in one patient in group B Heart rate, cardiac index and right ventricular end-diastolic volume index remained stable during the study period. Systemic vessel resistance index decreased significantly in group B (−18 ± 7% and −20 ± 12% from baseline 20 and 30 min after spinal puncture). The almost identical increase of wedge pressure following fluid administration demonstrates the employment of equieffective fluid regimes in this study (Figure)

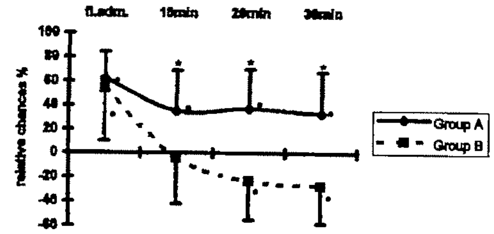

Table. Relative changes in wedge pressure after fluid administration, 10, 20 and 30 min after spinal puncture. *p < 0 01 between and °p < 0 05 insider the study groups

Conclusion: A single Infusion of hetastarch 6% (8.3 ml/kg in our study) prior to spinal puncture compensates hemodynamic effects during spinal anesthesia. Cardiovascular reactions after spinal anesthesia are only caused by a decrease of peripheral resistance and not by cardiac output.

A.365 Effects of preloading with NaCl 0.9%, HES (450/0.7) 6% and NaCl 3% on haemodynamic changes and serum osmolality in patients undergoing TURP under spinal anaesthesia

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Introduction: Fluid preloading is a commonly used method to prevent the hypotension during spinal anaesthesia In this study, we compared the effects of 0 9%NaCl, 6%HES and 3% NaCl given as a preload in maintaining haemodynamic stability in patients undergoing transurethral resection of the prostate (TURP) under spinal anaesthesia

Methods: After obtaining local hospital Ethics Committee's approval and informed consent, 36 male patients (ASA I–III) were randomly allocated to three groups Patients in each group were given 0.9%NaCl (2 meq/kg), 6% HES (7 ml/kg) and 3% NaCl (2 meq/kg) as preloading fluid before spinal anaesthesia, respectively Heart rate (HR), Mean arterial pressure (MAP) were measured by datascope and central venous pressure (CVP), cardiac index (CI), end-diastolic index (EDI) and systemic vascular resistance index (SVRI) were measured noninvasively by transthoracic electrical bioimpedance (TEB), and measurements were recorded before preloading (control), and 1, 5, 10, 15, 20, 25, 30, 45 and 60 minutes after preloading

Osmolality was calculated using the Na^+, K^+, blood glucose and BUN values measured before preloading and 1, 30 and 60 minutes after preloading. Statistical significance was determined by Student's t test

Results: There was no significant difference between three groups regarding HR, CI and SVRI values. CVP, MAP and EDI were higher in the 6% HES and the 3% NaCl groups compared with the 0 9% NaCl group (p < 0.05) While serum Na^+ and osmolality decreased at 30 and 60 minutes in the 0 9% NaCl group and at 60 minutes in the HES group, there was no decrease in the 3%NaCl group

Conclusions: We conclude that HES and 3% NaCl can be used as a safe preloading agents in patients undergoing spinal anaesthesia in maintaining cardiovascular stability. 3% NaCl can also decrease the risk of dilutional hyponatremia seen in TURP procedures

A.366 Puncture technique and postural post-dural puncture headache

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Background: The study was conducted in order to investigate the effect of the orientation of the bevel during dural puncture on the occurrence of PPDPH using a 0 42 mm (27 g) Quincke needle

Materials and Methods: 199 patients, aged 18–50 years, scheduled to non-obstetric infraumbilical surgery using spinal anaesthesia (SA) were included in the study The study was approved by the regional ethical committee, and informed consent from each patients was obtained in advance Patients were block randomized into two groups· A *parallel* group (with orientation of the bevel during dural puncture parallell to the longitudinal dural fibers) and a *perpendicular* group (orientation 90° angle to the fibers) Dural puncture were performed using a midline approach, with the patients usually in the lateral semiflexed position In all patients a 0.42 mm (27 g) Quincke needle (Braun or BD) was used. Anaesthetic agent was selected according to the anticipated length of surgery, using either hyper- or isobaric lidocaine or bupivacaine

Patients were blinded to the puncture technique, and so was an anaesthesiologist performing a telephone interview 5–7 days postoperatively. Using a semi structured interview the patients were asked about postoperative complaints in general, and headache and backache in particular PPDPH was defined as headache occurring postoperatively, usually after mobilization, relieved by lying down and aggravated when sitting or standing. Intensity of PPDPH and non-PPDPH was measured using a numeric rating scale from 1–10 (1 being no pain and 10 the worst pain imaginable)

Results: 194 patients were fully evaluable The reason for exclusion from the study are· Unable to contact postoperatively n = 2, no CSF found during dural puncture (patient given general anaesthesia) n = 1, one patients denied participation after randomization and one SA given by a trainee.

Mean age of the patients was 35 2 years. The two groups were comparable regarding age, sex, operating procedures performed, operating time and use of local anaesthetics PPDPH occurred in 4/97 (4 1%) in longitudinal group compared to 22/97 (22 6%) in the perpendicular group (p = 0.0007 Chi Square test) The 95% confidence interval of difference in PPDPH (18 6%) between the groups are 9 3–27 8%

Non-PPDPH occurred in 8 and 7 patients and backache in 28 and 18 patients (longitudinal compared to perpendicular group, NS)

Conclusions: When using Quincke needles orientation of the bevel is an important risk factor for the development of PPDPH even with small diameter needles. When using such needles care must be given to assure that the orientation of the bevel is parallell to the longitudinal dural fibers during dural penetration.

A.367 Unilateral spinal anaesthesia. Effects of needle design

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Background: In a search of an asymmetrical spinal block between surgical and non-surgical sides, we evaluated in a double-blind fashion the influence of needle tip on lateral distribution of hyperbaric bupivacaine in 30 patients scheduled for one leg surgery.

Methods: Patients were placed in the lateral position with the operated side dependent; then they were randomly allocated to receive 8 mg of 0 5% hyperbaric bupivacaine injected over 30 sec through a 25-gauge Whitacre (Whitacre, n = 15) or Quincke (Quincke, n = 15) spinal needle (Becton-Dickinson, New Jersey, USA) Before injecting the local anaesthetic solution, the needle bevel was turned toward dependent side of spinal canal Lateral position was maintained for 15 min. A blind observer recorded the progression of sensory and motor blocks on both sides The presence of an adequate sensory and motor block on surgical side, without one or both blocks on non-surgical one was considered as unilateral spinal anesthesia. Mann-Whitney test and Fisher exact test were used as indicated A value of P < 0 05 was considered as significant.

Results: Only one patient in Quincke group required general anesthesia due to inadequate spinal block (P > 0.05). Main results are presented in the table

	Whitacre (n = 15)	*Quincke* (n = 15)
Unilateral sensory block	10 (66%)	2 (13%)[$]
Unilateral motor block	11 (73%)	6 (40%)

[$] P < 0 01 vs Whitacre

Sensory block was 20% longer on operated side in 11 and in 8 patients respectively in Whitacre and Quincke groups (P > 0.05), while motor block was 20% longer on operated side in 13 and in 12 patients respectively in Whitacre and Quincke groups (P > 0 05),

Conclusion: When low dose of 0 5% hyperbaric bupivacaine and low speed of intrathecal injection are used in patients lying lateral for 15 min, Whitacre spinal needle allows a more marked differential block of sensory nerve roots between surgical and non-surgical sides as compared to Quincke needle

A.368 Spinal local anaesthetics distribution with two different pencil-point needles

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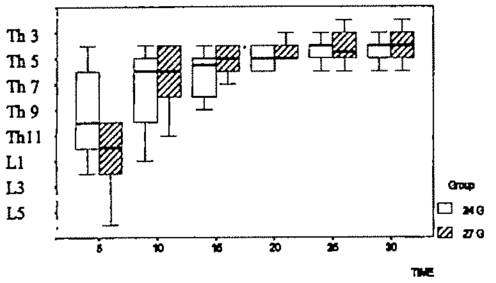
Background and Goal: Small gauge spinal pencil-point needles may lead to local anaesthetics maldistribution if injection is made in the caudal direction and if the injection speed is too slow (1). The purpose of this study was to evaluate the clinical distribution of local anaesthetics when injection was performed at a high rate and in a caudal direction through two different gauge pencil-point needles

Materials and Methods: After ethic committee approval and verbal patient consent, 20 ASA I or II patients scheduled for orthopaedic surgery of the lower limbs were randomised in two groups The two groups received a standard infusion line with Ringer-lactate solution. All patients were monitored using a single lead ECG, SpO_2 and NIBP during the procedure Spinals were performed in a sitting position at the L2–L3 interspace We injected 3 ml (15 mg) hyperbaric bupivacaine in a caudal direction in 10 seconds in both groups. We used a $27G3^{1/2}$ Whitacre needle for one group and a 24 G Sprotte needle for the second group. Patients in both groups were placed supine four minutes after spinal injection Sensory block levels were measured with ether in the midline at 5, 10, 15, 20, 25 and 30 minutes after spinal injection Hypotension, as defined by a 20% decrease from baseline or by a systolic blood pressure below 100 mmHg, was treated with ephedrine, atropine or phenylephrine according to the heart rate.

Results: The two groups were demographically comparable. Median sensory block levels at 30 minutes were at Th 4 in both groups (see figure)



Conclusions: Our study shows that spinal local anaesthetics distribution at a fast injection rate and in a caudal direction is uniform with a 27 G Whitacre needle compared to a 24 G Sprotte needle

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A.369 Advantage of multiple nerve stimulation in the axillary brachial plexus block

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Background & Goal of Study: The axillary approach to brachial plexus is the most popular for hand and forearm surgery The use of multiple stimulation approach improve the successful rate of axillary brachial plexus block (ABPB). However this technique has been principally evaluated by experienced anaesthetists working in hand surgery units (1). The aim of this study was to assess the success rate of ABPB according to the number of nerve stimulation and to the physician experience in a non hand surgery specialized center.

Materials & Methods: 287 brachial plexus blocks, between dec 94 and dec 96, were retrospectively studied. 209 ABPB were performed for hand and forearm surgery by experienced physician and by resident. Neural block was realised using a 22G insulated 50 mm bevelled needle and a peripheral nerve stimulator (Stimuplex, B Braun Medical). By axillary approach, one, two or three nerves (median, ulnar, radial, musculocutaneous) were located and blocked. The musculocutaneous nerve was never blocked alone. All patients received, in one or more injections, a total of 30 ml to 50 ml of lidocaine 1.5% with epinephrine 1:200 000 for the block. For each nerve, the stimulation eliciting muscle contraction was equal or less than 0.5 mAmp ABPB was considered unsuccessful if general anaesthesia or supplemental peripheral nerve block were required. Statistical analysis consisted of the χ^2 test and bilateral Fisher's exact test for qualitative variables. A p value < 0.05 was considered significant.

Results & Discussion: There were no differences in demographics data between groups No complications were noted The overall successful rate was 64.6% (135/209) and increased regarding the number of nerve stimulation (table). When physician experience was taken into account, the number of stimulation remained an important factor of success as show in table.

Nerve blocked	Success	Resident	Physician
One	48 3% (28/58)	41 9% (13/31)	55 6% (15/27)
Two	67% (61/91)	51% (24/47)	84% (37/44)
Three	76 7% (46/60)	70 4% (19/27)	81.9% (27/33)

Conclusion: Our study demonstrate that the success rate of ABPB increase with the number of stimulation independently of physician experience This approach of ABPB should be develop particularly in teaching hospital.

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A.370 Effects of surgical position on pulmonary function in patients with diaphragmatic paresis due to interscalene brachial plexus block

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Background and Goal of the Study: Surgical procedures of shoulder may be performed in different surgical positions We studied the effects of position on ventilatory function in patients with diaphragmatic paresis due to interescalene brachial plexus block (IBPB)

Materials and Methods: After informed consent, 6 ASA I patients scheduled for upper extremity procedures The patients were not premedicated and IBPB was performed after localization with an electrical nerve stimulator Forty ml mepivacaine 1.5% was injected. All patients were studied in 3 different positions, the order of each position was randomised, (sitting – Si, supine – Su, and lateral – La). Spirometry was performed before (T0) and 10 minutes after the block (T1), in two subsequent efforts in each position We measured forced vital capacity (FVC) and forced expiratory volume in first second (FEV1). Respiratory rate (RR) and SpO2 were also recorded. The parameters were compared using the Wilcoxon signed rank test

Results: The mean age, height and weight were 38 ± 11 years, 168 ± 5 cm and 74 ± 7 kg respectively. The table shows the mean ± S.D. values of FVC, FEV1, RR and SpO2.

		FVC (ml)	FEV1 (ml)	RR (b/min)	SpO2 (%)
Si	T0	2762 ± 219	2188 ± 153	15 ± 2	97 ± 1
	T1	$1883 \pm 427^{*}$	$1730 \pm 426^{*}$	19 ± 5	95 ± 1
Su	T0	2523 ± 252	2105 ± 151	14 ± 2	97 ± 1
	T1	$1323 \pm 406^{*+}$	$1088 \pm 259^{*+}$	18 ± 6	$95 \pm 1^{*}$
La	T0	2543 ± 253	2077 ± 148	15 ± 2	97 ± 1
	T1	$1518 \pm 606^{*+}$	$1203 \pm 407^{*+}$	$19 \pm 2^{*}$	96 ± 2

* $p < 0.05$ with respect T0, $^{+}$ $p < 0.05$ with respect Si.

The table shows that mean values for FVC and FEV1 were significantly higher in the sitting position on T1 compared with the supine and lateral positions.

Conclusion: This suggest that sitting position may be the best surgical position during shoulder procedures under interscalene brachial plexus block.

A.371 Superficial microcirculatory effects of interscalene plexus block

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Background and Goal of the Study: The excellent motor and sensory block by interscalene brachial plexus block is well described, but few data are available on the associated sympathetic blockade. The purpose was to analyze micro-circulatory events attributable to changes in sympathetic vasoconstrictor tone.

Materials and Methods: Eight patients (age 38–65; ASA I–II; seven male and one female) scheduled for acromioplasty under standardized anesthesia were studied. A unilateral interscalene plexus catheter was inserted preop. into the perivascular sheath, using the technique described by Winnie At the end of anesthesia, all patients received bupivacain as a bolus (1.25 mg/kg) followed by a continuous infusion (0 25 mg/kg/h) for postoperative analgesia. Three descriptors were used for the evaluation of sensory (sharp, blunt and dull) and motor block (normal movements, partial block and total block). Superficial blood flow (BF) was assessed by noninvasive laser Doppler (Periflux PF4001, Perimed, Sweden) and a probe (PF 408, Perimed, Sweden), placed at the skin on the index fingers of both arms Blood flow responses to apnea (APN, at end-inspiration after a deep breath), local index finger heat provocation (HP, probe heater PF 206, Perimed, Sweden) and skin temperatures were determined.

Statistics: 2-way ANOVA and Tukeys HSD test were used for comparisons between the arms.

Results and Discussion: Interscalene brachial plexus block showed an almost complete sensory and motor block In the following respects did observations in the *blocked arm* significantly differ from those in the un-blocked arm (data shown for 0, 2 and 4 hours respectively) a) baseline BF was higher (by 350%, 265% and 165% resp), b) the increase in BF by HP was reduced (by 166%, 145%, 175% resp), c) APN induced a less pronounced decrease in BF (by 32%, 32% and 41% resp.) and, d) skin temperature was higher (by 5 7 ± 0 4, 6 7 ± 0 7° and 5 0 ± 0.7°C resp.).

Conclusions: Interscalene brachial block, besides producing sensory and motor block, increase superficial blood flow, skin temperature and reduce the regional circulatory effects to apnea after a deep breath and to heat provocation. We suggest, that this reflects a reduced neurogenic vascular tone and, as regards the latter observation, a reduced local vasodilatory reserve on the blocked side The laser Doppler flowmetry technique appears to be a useful tool for studying the sympathetic blockade following regional anesthesia

A.372 Does a distal infection of the upper limb interfere with the success rate of axillary block?

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Background and Goal of Study: It has already been demonstrated that tissue acidosis associated with infection modifies the local anesthetic dissociation, leading to incomplete anesthesia[1] Whether the presence of a distal infection of the upper arm may influence the success rate of axillary block is unknown To examine this hypothesis, we compared the quality of anesthesia for surgery under axillary block in the presence or in the absence of a distal infection

Material and Methods: To evaluate the failure rate of regional anesthesia, the need for supplementary blockade of peripheral nerves, sedation, or general anesthesia was investigated in 25 patients with a distal infection (group A) and in 30 patients with no infection (group B) This study was retrospective and performed during a two-years period (1996–97). The radial, median, and musculo-cutaneous nerves were localized with a nerve stimulator. A mixture of 0.5% bupivacaine and 1% lidocaine (1:1) with 1 ml clonidine (0.150 mg) was injected at each localisation, with a total dose of 41 ml

Results and Discussion: There were no statistically differences between the two groups of patients, according to age (mean age = 44 in group A, 49 in group B), sex and ASA scores The results of our study are showed in the following table:

Group	Number of patients	nb (%) of patients requiring		
		additional nerve blockade	sedation	general anesthesia
Infection (A)	25	2 (8%)	1 (4%)	2 (8%)
No infection (B)	30	1 (3%)	1 (3%)	2 (7%)

Conclusion: The success rate of axillary block was identical in the two groups (80% in the groups with infection, 87% in the group without infection). The presence of a distal infection did not interfere with the quality of anesthesia in our study. These preliminary results and the rate of local complications (particularly axillary abscess) should now be confirmed by a prospective and randomized study.

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A.373 Cervical plexus block for carotid endarterectomy: influence of locoregional technique

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Background: Cervical plexus block (CPB) is an effective technique in carotid endarterectomy (CE). However, local anesthetic injection in this highly vascular area may be responsible for important systemic resorption and/or accidental intravascular injection We compared two local anesthetic techniques for CE: Interscalene Block (ISB) performed with only one injection and the classical CPB.

Methods: 23 ASA II–III patients undergoing CE were randomized to received either ISB (n = 12) or CPB (n = 11). The deep CPB was performed with 20 ml 0.5% of plain Bupivacaine (B) and was assisted by a complementary superficial CPB with 20 ml of 2% plain Lidocaine (L). ISB was performed under nerve stimulation control with a single injection of 20 ml of 0 5% B combined with 20 ml of 2% L Duration of injection to achieve ISB or CPB were standardized to two min. Evaluation of pain (VAS 0–100) was performed during anesthetic and surgical procedure. Additional requirement of analgesic and sedative agents were recorded Arterial blood samples were collected, before and 3, 5, 8, 10, 15, 25, 40 and 60 min. after the beginning of the block in the two group. Plasma concentration of L and B were measured by high performance liquid chromatography Pharmacokinetic parameters included peak plasma concentration (CMax) and the time to reach the peak (TMax) calculated on individual observed data Values (Mean ± SD) were compared using the Mann and Whitney U test

Results: Demographic parameters were comparable in the two groups Satisfactory pain relief was obtained in all patients No serious adverse events were noted The plasma concentrations of L and B are summarized in the table. CMax of B is significantly decreased in ISB group No significant difference was found in CMax of L between the 2 groups TMax of B and L increased in ISB group

Discussion: In our study, the AL systemic resorption of CPB is no different from results found in previous studies [1] Since systemic toxicity of LA depends of C Max but also of the speed with C Max is reached, the results or of studies suggest that ISB is probably a safe procedure

L et B plasma concentrations (Mean ± SD)

	L		B	
	CPB	ISB	CPB	ISB
C Max (μg/ml)	5 65 ± 1 86	4 84 ± 2 12	1 64 ± 0 70	1 06 ± 0 47*
T Max (min)	11 73 ± 3 93	17 08 ± 4 98*	11 00 ± 3 87	19 17 ± 8 2*

* P < 0 05 *vs* CPB

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A.374 Cervical plexus block with ropivacaine for carotid endarterectomy

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Background and Goal of Study: The use of regional anesthesia for carotid endarterectomy was first suggested to check the patient's neurologic status during carotid cross clamping Since 1984 to 1994 we had employed the technique described by Moore(1) for carotid surgery in every patient Since 1994 we have been applying a new technique, consisting of the use of an electroneurostimulating device to detect the cervical nerves(2) Recently we have employed Ropivacaine, a new anesthetic solution available in different concentrations (2–7.5–10%), presenting a duration of action as long as bupivacaine, a lower cardiotoxicity and an earlier onset of action(3) We employed 7.5% Ropivacaine for carotid surgery to assess its pharmacologic efficacy, duration of action and complications

Material and Methods: Over a 6-month period, 50 ASA I–III patients (38 males and 12 females) undergoing carotid endarterectomy were prospectively studied Average age was 69. The anesthetic block was performed upon the C_3 transverse process, injecting up to 12–15 ml of 7 5% Ropivacaine (90–112.5 mg) Paresthesias and/or muscle contractions over the C_3 nervous area, in the nape and lateral region of the neck, were searched before injection Moreover, the superficial cervical plexus block was performed using 10–12 ml of 1% mepivacaine, according to Moore's technique The intervention began 10–15 minutes after the end of the block Analgesia was evaluated by a visual analogous scale.

Results: No patient complained of trouble from elettroneurostimulation and none underwent general anesthesia for incomplete analgesia During the surgery, sedation was provided with fentanyl (0.05–0 1 mg) in 22 patients (44%), to make them more tolerant but preserving their cooperation. Analgesia lasted enough to perform the intervention even when it sometimes lasted more than 120 minutes 40 (80%) patients valued analgesia as excellent or good, 10 (20%) as sufficient, whereas anesthesia was supplemented with local infiltration in the carotid sheat with mepivacaine in 6 patients (12%). No complication due to ropivacaine itself was shown intraoperatively, 8 patients (16%) presented hypertension Other patients developed transient hypotension (8%) and bradycardia (8%), these signs were caused by surgical stimuli of carotid glomus, as they promptly disappeared after the suspension of the surgical stimulus and the administration of vagolitic and/or vasoactive drugs 5 patients (10%) developed transient dysphonia, due to the anesthetic block of the recurrent laryngeal nerve

Conclusion: 7.5% Ropivacaine has been shown to be as effective as Bupivacaine for carotid surgery, as regards duration of action and efficacy The low toxicity suggests the use of Ropivacaine instead of Bupivacaine.

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A.375 Are muscle relaxants to be used in regional intravenous anaesthesia?

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Introduction: This research was planned to determine and compare the effects of addition of different muscle relaxants into local anaesthetic solutions that are used in Regional Intravenous Anaesthesia (RIVA)

Method: Fifty-one patients who had undergone hand and forearm surgery were included to this research with the approval of the ethic committee. Patients were divided into 3 groups of random after motor activity was measured with a manometer at the extremity of interest Classical RIVA was performed by using 3 mg/kg 0 5% lidocaine (LA, n = 16) in group 1, 3 mg/kg 0.5% lidocaine + 50 μg/kg atracurium (LAT, n = 16) in group 2 and 3 mg/kg 0 5% lidocaine + 7 μ/kg vecuronium (LAV, n = 20) in group 3. Heart rate, blood pressure, motor activity and sensorial blockage measurements were evaluated at the 1st, 5th, 10th and 15th minutes. Touching and pain senses were scored as blockage (+) = 0 and blockage (–) = 1 at 5 different sites and the mean values were calculated. After the blood pressure and heart rate were recorded at the end of the operation, the tourniquet cuff was release. Additionally, anaesthesia quality and muscle relaxations were evaluated and scored by the surgeon The results were analyzed with ANOVA, Mann-Whitney-U, Wilcoxon, chi-square tests, $p < 0.05$ was accepted as significant

Results: There was no difference in demographic properties, initial motor activity, tourniquet pressure, tourniquet and operation duration between the groups, 1, 5, and 10 minutes after the local anaesthetic administration, there happened a significant difference in motor activity between the groups. Motor blockage was placed at the 1st minute in group LAV at the 5th minute in group LAT, at the 10th minute in group LA. No difference was determined between the groups by means of sensorial blockage The median value for touching sense in all groups became zero at the 15th minute of local anaesthesic injection. The median value for pain sense in group LA and LAT was zero at the 5th minute and in group LAV, it was zero at the 10th minute. In the surgeons' scoring, there was no difference between the groups by means of anaesthesia quality and muscle relaxtions.

Conclusion: Our result indicated that combination of muscle relaxants accelerate the motor blockage, but even in the group LA, complete motor blockage was placed while waiting for the sensorial blockage. On the other hand, combination of muscle relaxants did not provide additional comfort for the surgeon For the reasons, combination of muscle relaxants to lidocaine solution is not considered to be useful application in RIVA.

A.376 Clonidine and lidocaine *vs* lidocaine for intravenous regional anaesthesia

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Background and Goal of the Study: As clonidine can enhance the effects of lidocaine on C-fiber action potential (1), this double-blind, randomised, study was designed to examine the effects of the addition of clonidine 150 μg to 40 mL lidocaine 0.5% for IVRA.

Materials and Methods: After informed consent and institutional approval, 24 ASA-1 patients, scheduled for minor hand surgery, were studied during an IVRA performed with a double-cuffed tourniquet. Proximal cuff was inflated first (7 cm wide; 250 mmHg) and switched to the distal cuff (7 cm wide, 250 mmHg) if the patient complained of tourniquet pain. The test drugs, i.e. either saline (n = 12) or clonidine (n = 12) at random, were injected with lidocaine in the arm after its exsanguination using an Esmarch bandage. Duration of pain tolerance, defined by the time elapsed between inflation and deflation of the proximal cuff, was measured, as well as tourniquet and forearm pains using a visual analog scale, blood pressure, heart rate and sedation, before and 15, 30 and 45 min after injections. Statistics were Mann-Whitney tests and ANOVA *P* was set at 0.05.

Results and Discussion: Duration of pain tolerance was greater in the Clonidine group (27 ± 15 *vs* 14 ± 6 min, $p < 0.01$). Tourniquet and forearm pain scores and systolic arterial pressure were greater in the saline group (Table). Systolic and diastolic arterial pressure increased only in this group ($p < 0\ 01$) There were no changes and no differences between groups for sedation and heart rate

	Before	15 min	30 min	45 min
Tourniquet pain score (0–100) *median; range*				
Saline	0, 0–0	40, 10–70	40, 20–60	50, 30–70
Clonidine	0, 0–0	20, 10–50*	25; 20–30	30, 20–40*
Forearm pain score (0–100) *median, range*				
Saline	0, 0–0	25, 0–50	30, 10–40	35; 20–50
Clonidine	0; 0–0	15, 0–20	15, 0–30*	20, 0–30*
Systolic arterial pressure (mmHg) *m ± SD*				
Saline	132 ± 6	140 ± 4	140 ± 5	141 ± 6
Clonidine	133 ± 8	135 ± 5*	137 ± 5	136 ± 6

* $p \leq 0\ 05$ comparisons between groups

Conclusion: Clonidine may improve IVRA with 0.5% lidocaine, both in terms of controlling intraoperative pains and by blunting hypertensive response to tourniquet

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A.377 Is ropivacaine 0.2% an alternative to lidocaine 0.5% for intravenous regional anaesthesia?

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Introduction: Intravenous regional anaesthesia (IVRA) may be used to anaesthetize the upper limb for a variety of surgical procedures Lidocaine 0.5% is most frequently used for this purpose. Recently ropivacaine was introduced and was shown to produce only minor side effects following intravenous injection (1). We investigated if ropivacaine would produce equal efficient surgical anaesthesia as lidocaine when used for IVRA.

Methods: Following IRB approval, ten healthy, unpremedicated volunteers participated in this randomized, double-blind, cross-over study receiving 40 ml of either plain lidocaine 0 5% or plain ropivacaine 0.2% for IVRA, at least four days apart Pain assessments were made using a verbal numeric scale (VNS), from 0 = no pain to 10 = worst imaginable pain in response to a 50 Hz tetanic stimulus of 60 mA. This has been shown to be an equivalent stimulus to surgical incision (2). Loss of sensation was evaluated by pinprick. Motor function was evaluated using a blood pressure cuff that was inflated to 40 mmHg and which the volunteer was asked to squeeze maximally Following exsanguination, the proximal portion of a double-cuff tourniquet was inflated to a pressure of 250 mmHg When the proximal tourniquet pressure became unbearable and was rated 10 on the VNS, the distal cuff was inflated followed by release of the proximal tourniquet The distal tourniquet remained inflated until a VNS score of 10 was reached again. Measurements were performed prior to, and every 5 min during tourniquet inflation as well as 3, 10, and 30 min (table) after release of the distal tourniquet. Following deflation of the distal tourniquet, the volunteers were questioned about CNS side effects and asked to rate them on a VNS between 0–10. Simultaneously, ECG changes from baseline were recorded. Data are expressed as mean ± SD and were analyzed using Wilcoxon rank and paired t-tests for non-parametric and parametric data, respectively; $p < 0.05$ was considered statistically significant

Results: There were no significant differences between the two local anaesthetics with respect to tourniquet tolerance and onset time of surgical anaesthesia Motor bock set in earlier and recovered faster with lidocaine than ropivacaine after release of the distal tourniquet ($p < 0.05$, table). Recovery of sensation to pinprick took longer with ropivacaine than with lidocaine ($p < 0.05$) CNS side effects were more prominent after lidocaine than after ropivacaine ($p < 0\ 05$).

Discussion: Ropivacaine 0 2% has similar features as lidocaine 0.5% with respect to surgical anaesthesia and tourniquet tolerance. As a long acting local anaesthetic it generated a better analgesia and longer motor blockade after tourniquet release than lidocaine. Most importantly, side effects were substantially less pronounced than with lidocaine, making ropivacaine a potential alternative for use in IVRA.

Recovery of sensory and motor function (% of baseline)

	Sens3	Sens10	Sens30	Mot3	Mot 10	Mot 30
Lido	71 ± 31	89 ± 15	94 ± 12	65 ± 21	79 ± 18	87 ± 16
Ropi	52 ± 35	65 ± 31	78 ± 28	45 ± 13	60 ± 23	65 ± 25

A.378 Total knee replacement: a comparison of ropivacaine and bupivacaine in combined femoral and sciatic block

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Background & Goal of Study: This study was designed to compare post-operative analgesia provided by femoral and sciatic nerve block following total knee replacement using either bupivacaine or ropivacaine. A control group received no blockade.

Materials & Methods: Following Ethical Committee approval, informed consent was obtained from 60 ASA 1–3 patients scheduled for elective unilateral primary total knee replacement. Oral diazepam 10 mg was administered 1 hr pre-op. Spinal anaesthesia was administered with 2.0–3.0 ml 0.5% heavy bupivacaine + 0.75 mg diamorphine with the operative side down. Patients were then randomised into one of three groups. Group A received no further intervention. Group B received 2 mg/kg 0 75% bupivacaine divided equally between the femoral and sciatic nerves. Group C received 2 mg/kg 0 75% ropivacaine divided equally between the femoral and sciatic nerves. All nerve blocks were carried out by an anaesthetist blinded to the grouping using a Braun Stimuplex with a 22G insulated needle. Time to first morphine, morphine consumption and VAS pain scores were assessed at 4 hrly intervals by nursing staff blinded to group allocation.

Results: Time to first morphine consumption was significantly longer in groups B and C than group A. Morphine consumption was significantly reduced at all times in group B compared with group A Morphine consumption was significantly reduced for the first 28 hours in group C compared with group A There were no significant differences in morphine consumption between groups B & C. There was no significant difference in pain scores between the two groups. (ANOVA analysis, $p < 0\ 05$ as significant).

Conclusions: Additional femoral and sciatic nerve blockade with either bupivacaine or ropivacaine following spinal anaesthesia provided prolonged analgesia when compared spinal anaesthesia alone. Bupivacaine provided a greater reduction in morphine consumption than ropivacaine.

A.379 Anterior approach to sciatic nerve block: a new landmark

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The anterior approach to the sciatic nerve block offers several advantages. 1) it requires no change in the patient's position to perform other blocks of the lower limb, 2) it causes no discomfort or hazard to the traumatized patient However, this technique is considered difficult and at risk of damaging major blood vessels (1). Here we describe a new anterior approach to the sciatic nerve With the patient laying supine and the lower extremity in neutral position, the great trochanter was identified and marked (G) From this point, a straight line (GX) of 10 cm, parallel to the femoral shaft, was drawn, and the end point marked (X). Afterwards, the medial edge of the patient's rectus femur muscle was identified by muscular contraction and lined. The intersection between this line and the line perpendicular to GX segment, meeting point X, was the point of injection. The sciatic nerve was identified by a peripheral nerve stimulator-aided technique. A 20–21 G short bevel, 15 cm long, insulated needle was used in all cases. When the tip of the needle met the anterior medial surface of the femur, the needle was withdrawn to the subcutaneous tissue and redirected perpendicularly until a muscular activity was evoked in the tibial and peroneal nerve supply (usually at a depth of 9–12 cm). Then, 30 ml of mepivacaine 1% plus adrenaline 1/400.000, alkalinized 1/10 with sodium bicarbonate 8 4% were injected First we performed the block of the femoral, lateral femoral cutaneous and obturator nerves with 30 ml of the same anesthetic solution, then the block of the sciatic nerve, in order to minimize the patient's discomfort (the thigh is already anaesthetized). The block was used, after informed consent, on 114 patients (70 males, 44 females) undergoing orthopaedic surgery of the lower limb (arthroscopy = 90, tibial osteotomy and osteosynthesis = 11, tendon repair = 8, others = 5). The block was complete (no discomfort during surgery) in 89 5% of the patients, and fair (supplementation with sedatives and/or narcotics or peripheral local anaesthesia) in 7%. In 4 cases (3.5%) the block failed, and a posterior approach was necessary. Therefore sciatic nerve was identified on the first attempt in 18 cases, on the second in 43, on the third in 32, on the fourth in 17 cases The mean dose of mepivacaine injected was 8 10 mg^*kg^{-1} (range 5.3–12) The time of onset was 7 1 ± 3.4 min (range 4–20), the latency of complete block was 11 9 ± 4.5 min (range 6–25). The duration of anaesthesia was 272 ± 73 min, while that of analgesia was 290 ± 72 min. The degree of anaesthesia was always adequate for applying a tourniquet without pain. Our modified technique had high acceptance by the patients (91.2% very satisfied, 8 8% enough satisfied), especially in subjects with lower extremity fractures. During the study, neither clinically relevant side effects nor sequelae were observed. In conclusion, our technique of anterior sciatic nerve block proved to be reliable, easy and safe for lower limb surgery (except for femur).

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A.380 Continuous popliteal sciatic nerve block catheter: incidence of complications

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Background and Goal of Study: CPSNBC is an efficient and reliable postoperative analgesia technique after major elective foot orthopedic surgery (FOS). The aims of the study were to identify the incidence of complications with this technique.

Materials and Methods: After informed consent, patients (P) were prospectively studied Before spinal anesthesia and surgery, catheter (C) (Contiplex°, France) was inserted (ventral position) (VP) in the popliteal fossa (1) using a neurostimulation technique (2) An initial bolus was injected, followed by a constant infusion of bupivacaine 0 125%, 10 ml/h We noted: time (T) to inserted C (T between the operator begin to wash his hands to the end of the procedure), immediates complications, complications over 48 h, and 3 weeks later

Results and Discussion: 21 P (8 males, 13 females, 69 ± 13 kg, 169 ± 10 cm; 45 ± 20 years).

(1) Technique of insertion· No P refused to stay in VP Mean T· 16 mn (SD: ± 7.5 mn) Mean stimulation· 0 3 mA (always <0 5 mA).

(2) Immediate complication No vascular ponction, no failure (included reaseach of sciatic nerve), no difficulty to injected, no paresthesia were observed. No difficulty to inserted the C in the popliteal fossa up to 5 to 10 cm in the perinervous space.

(3) Complications after 48 hours· 1 motor block (stopped at the end of perfusion), 3 C culture + without any incidence, mean morphine consumption: day one: 2.4 mg (SD· ± 3 5); 0 mg for 15 patient (EVA < 30) Day 2· 2.6 mg (SD. ± 6 1); 0 mg for 13 P. No accidental withdrawal C.

(4) No nervous complication after 3 and 6 weeks

For next surgery, all patients will accepted CPSNBC

Conclusion: The efficient and very low rate of complications with CPSNBC might be an interesting challenge for major FOS surgery.

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A.381 Continuous analgesia with a femoral catheter: plexus or trunk blockade?

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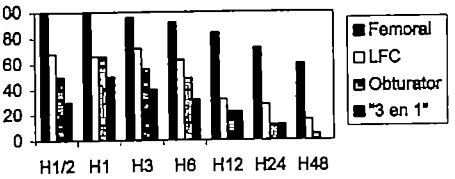
Background & Goal of Study: Commonly, physicians using a femoral catheter for postoperative analgesia after hip or knee surgery consider that they produce a continuous lumbar plexus blockade [1, 2]. Nevertheless, none of them perform a neurologic testing to prove it The aim of this study was to evaluate the extent of sensory blockade produced by a continuous infusion in a femoral catheter throughout a 48 H period

Materials & Methods: After informed consent, 20 patients scheduled for major knee surgery were prospectively included Following a standardized general anesthesia, a femoral catheter was introduced and advanced 12–15 cm cephalad in the femoral nerve sheath, using a nerve stimulator. In the recovery room, a 30 mL bolus of 2% lidocaine with 1/200 000 epinephrine was given, followed by a 48 hours continuous infusion of 1% lidocaine + 0.03 mg/ml morphine + 2 μ/ml clonidine (rate. 0 1 ml/kg/hour)

The sensory blockade was assessed at H$\frac{1}{2}$, H1, H3, H6, H12, H24 and 48 H using the pinprick method in the femoral, lateral femoral cutaneous (LFC) and obturator nerves territories The quality of analgesia was assessed by using a visual analogic scale ranging from 0 (no pain) to 100 mm (worst possible pain) at the same times

Results & Discussion: The block produced by the 30 mL induction bolus was not constantly a "3-in-1" blockade (50% of cases in our study). While maintaining analgesia by a continuous infusion, sensory blockade affects the three main nerves of the lumbar plexus in less than 20% of patients after 6 hours Sensory blockade was limited to the femoral nerve in 44 to 52% of patients after 12 hours [figure 1] However, this sensory blockade provide effective pain relief and the median VAS values were lesser than 40 mm at any times in the study



Conclusion: Our findings contradict the commonly "continuous lumbar plexus block" appellation used in previous studies An isolated femoral nerve sensory blockade appears after several hours, sometimes associated with lateral femoral cutaneous and/or obturator nerves blockade. "Continuous femoral block" should be more appropriate to describe the prolonged use of a femoral catheter for postoperative analgesia

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A.382 Analgesia for total hip arthroplasty with posterior lumbar plexus block

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Background: Sensory afferents from the hip involve mainly the lumbar plexus (LP). Uncontrolled studies have shown that pain related to hip surgery can be effectively managed with LP blockade (1) However, the anterior "3-in-1" approach does not predictably block all major trunks of the LP, and the usefulness of this technique was questioned in a recent study (2) In this randomised controlled double blind trial, we evaluate the analgesic effect of LP blockade using a posterior approach.

Methods: After institutional approval and informed consent, 41 patients ASA I-III undergoing total hip arthroplasty were allocated general anaesthesia with (n = 21) or without (n = 20) posterior LP block. Block was performed after induction using a nerve stimulator (≤0.4 mA) and following Winnie's description (3), and 0.4 ml/kg bupivacaine 0 5% with epinephrine was injected. Intraoperatively, increments of fentanyl were administered as needed by a physician blinded to treatment allocation Postoperative pain (VAS) and PCA morphine consumption were assessed for 48 hours. Inadequate analgesia was supplemented in the PACU by boluses of i.v "rescue" morphine Means are given ± SD and groups compared using the unpaired Student's *t*-test or the chi-squared test as required

Results: Baseline variables in both groups were similar. Intraoperatively, the number of patients requiring additional fentanyl was >3 times higher in the group without the block (17/20 vs 5/21, $p = 0.02$). Upon arrival in the PACU, a fivefold reduction in mean pain scores was observed in patients receiving the block (VAS 1.1 ± 2.1 vs 5.7 ± 2 9, $p < 0.00001$) Rescue morphine was needed by 14/20 in the untreated group, against 1/21 in the group with the block ($p < 0.0001$). In the latter group, cumulative morphine consumption remained lower until 12 hours after administration of the block (13.1 ± 9.7 vs 19.7 ± 10.8 mg, $p = 0.04$) Epidural-like distribution was noted in 3/21 patients (14%) without adverse consequences.

Conclusions: LP blockade using the posterior approach offers effective pain relief after hip surgery. Our results also suggest a block-related intraoperative opioid-sparing effect The technique is safe but incidence of epidural-type spread is not negligible.

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A.383 Regional anaesthesia for femoral neck fracture surgery: comparison of lumbar plexus block and spinal anaesthesia

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Background & Goal: Regional Anesthesia does not significantly improve outcome of patients after femoral neck fracture surgery (1). A posterior LBP affords more theoretical benefits on commonly practiced Spinal Anesthesia. The aim of this study is to evaluate efficacy and safety of LBP in comparison with SA in patients undergoing femoral neck osteosynthesis.

Patients & Methods: Both techniques were prospectively evaluated in 50 patients randomized in two groups after Ethical Committee approval: 1) SA with single shot Bupivacaine 0 5%. 2) Posterior LPB as described by Winnie (2), with nerve stimulator, and mixture of equal volumes lidocaine 2% + bupivacaine 0.5% with 1:200,000 epinephrine A light sedation by propofol IV was associated in case of discomfort during surgery Results are presented as mean ± SD Statistical analysis used non-parametric tests.

Results: The two groups were similar with regard to age (82 ± 12 y), weight, ASA status, and duration of surgery No significant complications were observed.

	LPB n = 25	SA n = 25	p
Insertion difficulties	3	10	<0 05
Propofol > 1 mg/kg/h	19	5	<0 01
Mean Art BP > 20%	3	18	<0 01
Ephédrine (mg)	1 2 ± 2 7	7 0 ± 2 6	<0 001
VAS H + 3 (mm)	14 ± 16	20 ± 24	NS
VAS H + 8 (mm)	26 ± 18	38 ± 24	NS
Adverse effects	1*	6**	<0 01

*1 AL Tox **1 PPDH 5 urin ret

Discussion: This study confirms the easiness and safety of LBP as compared with SA. Though by itself insufficient to provide good anesthesia for hip fractures surgery, LBP appears to be more suitable than SA with regard to hemodynamic changes and adverse effects. Surgery could be performed under light sedation with propofol in spontaneously breathing patients Lack of difference in postoperative analgesia may be related to the small size of the population. It is concluded that LBP must be reevaluated in association with sciatic or high paravertebral block for surgery of femoral neck fractures.

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A.384 Clinical comparison between ropivacaine and bupivacaine for lower limb peripheral nerve block

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Background: The purpose of this prospective, randomized, double-blind study was to compare ropivacaine and bupivacaine during combined sciatico-femoral nerve block.

Methods: With Ethical Committee approval and patients' consent, 30 patients, ASA Physical status 1–2, scheduled for elective hallux valgus repair with thigh tourniquet were randomized to receive combined sciatico-femoral block by 0.75% ropivacaine (ROPI, n = 15) or 0 5% bupivacaine (BUPI, n = 15). For the femoral block 10 ml of anaesthetic solution were employed, while for the sciatic block 15 ml of the same solution were used. In order to obtain a correct localization of the block needle a nerve stimulator (Plexival, Medival, Italy) with insulated needles (Locoplex, Vygon, France) were used. A stimulation frequency of 2 Hz and a current ranging between 0.5 and 1 mA were used. Time required for onset of sensory and motor block and for resolution of motor block at operated foot, as well as onset of postsurgical pain and analgesics requirement were recorded. Mann-Whitney test and Fisher exact test were used as indicated A value of $P < 0.05$ was considered as significant

Results: The two groups were similar with respect to anthropometric parameters, duration of surgery and measured VAS pain scores. Main results are presented in the table

	ROPI (n = 15)	BUPI (n = 15)
Onset sens block (min)	14 ± 17	37 ± 27$
Onset mot block (min)	16 ± 10	51 ± 32$
Duration Analgesia (min)	670 ± 227	880 ± 312
Postop. Analgesics	7 (46%)	6 (40%)

$P < 0 001 vs RCPI

conclusion: This study demonstrated that 0 75% ropivacaine allows a latency of sciatico-femoral nerve block shorter than 0.5% bupivacaine with a prolonged postoperative pain relief

A.385 Ultrasonographic guidance reduces the amount of local anaesthetic for 3-in-1 blocks

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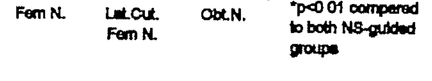
Background: Recently it has been demonstrated that the use of ultrasound (US) improves the sensory blockade and the onset time of 3-in-1 blocks as compared to conventional nerve stimulator (NS) guided techniques (1). This study was designed to evaluate if US guidance reduces the amount of local anesthetic.

Methods: After institutional approval and informed consent 45 patients undergoing hip surgery following trauma were randomly assigned and double blinded to three groups. In the US group the 3-in-1 block was performed under US guidance with 20 mL bupivacaine 0.5%. In the NS guided groups the 3-in-1 block was performed under the guidance of a NS with 20 mL and 30 mL bupivacaine 0.5%. The quality and onset time of the sensory block was assessed by pinprick test in the central sensory region of each of the three nerves and compared to the same stimulation on the contralateral leg every 10 min for 60 min. The rating was undertaken using a scale from 100% (uncompromised sensibility) to 0% (no sensory sensation). All results were expressed an mean ± SED. Statistical analysis was performed by ANOVA and Student's t-test A $p < 0$ 01 was considered significant.

Results: US guidance reduces significantly the amount of local anesthetic to achieve satisfactory levels of anesthesia. Onset time for 3-in-1



*p<0 01 compared to both NS-guided groups block in the US group was significant shorter as in both NS groups (US 13 ± 7 min, NS 20 mL 27 ± 14 min, $p < 0.01$ and NS 30 mL 26 ± 16 min; $p < 0.01$ to group US) The quality of sensory block was also significant better in the US group as compared to both NS groups (Figure).

Conclusions: The new US guided technique for 3-in-1 blocks has a better onset time and quality of sensory blockade as compared to the NS guided 3-in-1 when the same amount of local anesthetic were administered The increase of local anesthetic of 50% has no benefit for NS guided 3-in-1 blocks Therefore, US guidance reduces the amount of local anesthetic

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A.386 Comparison of the "3 in 1" and "fascia iliaca compartment" blocks in adults: clinical and radiographical analysis

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Background and Goal of Study: In children, the fascia iliaca compartment block was reported to provide respectively 100%, 92% and 88% of sensory blockade of the femoral (F), obturator (O) and lateral femoral cutaneous (LFC) nerves In adults the '3 in 1' block was shown to be inconsistent in producing blockade of both the LFC and O nerves. The present study was designed to compare these two approaches in adults

Patients and Methods: After institutional approval, 100 patients scheduled to undergo either hip, femoral shaft or knee surgery were randomly assigned, for the postoperative pain relief, to '3 in 1' (group 1) or fascia iliaca compartment (group 2) blocks After general anesthesia, once the patients were awakened and extubated, the '3 in 1' block was realised using an insulated needle and a nerve stimulator and the fascia iliaca compartment block following Dalens et al (1) technique. The local anesthetic solution used for all patients was 30 ml of an equal volume mixture of 2% lidocaine with epinephrine and 0.5% bupivacaine to witch 5 ml of contrast media was added Sensory blockade was evaluated in the three nerve territories using cold and pinprick tests at ten min intervals over the 30 min period following injection. At 30 min, motor blockade of the F and O nerves was assessed and a frontal pelvic region's radiograph was taken

Results: Two block failures were noted in group 2. Complete lumbar plexus block was achieved in 38% group 1 and 34% group 2 patients. Sensory blockade of the F nerve was obtained in 90% and 88%; of the O nerve in 52% and 38% and of the LFC nerve in 62% and 90% ($p < 0.05$) respectively in groups 1 and 2 Sensory LFC nerve blockade was obtained more rapidly in group 2 ($p < 0.05$) A motor blockade of F and O nerves was effective in 76% and 32% group 1 and 80% and 20% group 2 patients. The anesthetic solution reached the lumbar plexus in only 5 radiographs A concurrent internal and external spread, under the fascia iliaca, was noted in 62 of the 92 radiographs analysed. Isolated external spread, under the fascia iliaca and over the iliacus muscle, were noted in 10% and 36% of the patients in group 1 and 2 ($p < 0.05$) The O was never blocked in the external spreads.

Discussion and Conclusion: The fascia iliaca compartment block is more effective than the '3 in 1' block in producing simultaneous blockade of the LFC and F nerves in adults. Following both procedures, blockade was obtained primarily by the spread of local anesthetic under the fascia iliaca and only rarely by contact to the lumbar plexus.

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A.388 Improved regional blockade prolongation method from mixture of local anaesthetics

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Background & Objectives: Previous efforts to prolong the duration of local anesthetics by means of lipid carrier, liposphere, pellets, microspheres have concentrated on employing single local anesthetic[1–3]. Each local anesthetic has its own property. Lidocaine is pharmacologically safe and fast in onset time but has short action duration, while bupivacaine is a highly potent local anesthetic having comparatively slow onset time and higher side effect than lidocaine In this paper mixture of lidocaine and bupivacaine is formulated into pellet with a biodegradable polymer for improving the prolongation of nerve block by taking advantages of each constituent local anesthetic The formulated pellet was evaluated for its efficacy and safety

Materials and Methods: Pellet was prepared by a modified melting molding process[2] with 30 wt % poly (dl-lactide-co-glycolide), 35 wt % lidocaine and 35 wt % bupivacaine. In vitro release kinetic study was carried out by incubation of the pellet in phosphate buffered saline Released drug was assayed by high performance liquid chromatography Rat sciatic nerve model[3] was used for in vivo evaluation of the pellet using an analgesiometer. Local anesthetic dosage used was 70 mg/kg for lidocaine and bupivacaine, respectively One month after implantation, histological examination of the nerve tissue adjacent to the pellet was performed Sensory block data were analyzed by paired t-test using SAS 6.03

Results and Discussion: In vitro release profile demonstrated that both anesthetics released in controlled manner and lidocaine released in fast rate while bupivacaine relatively in slow rate. Approximately 80% of the total local anesthetics was released within 3 ~ 4 days Five male Sprague-Dawley weighing 250–300 g produced prolonged sciatic nerve blockade for periods lasting 3 days Previous study[2] using single bupivacaine with dose of 150 mg/kg resulted in prolonging the duration to 3–5 days This finding demonstrated that the mixture system is a improved method by reducing the dosage to half and obtaining almost equivalent effect All of the animals appeared to recover in 4 days Histology examination showed no evidence of nerve tissue damage

Conclusion: The results indicated that the mixture system showed a promising approach to improve the prolongation of local anesthetics

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A.389 Peroperative analgesic effects of clonidine and fentanyl administered by systemic and/or epidural routes

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Background & Goal: Opioids and α_2 agonists provide effective analgesia in different animal models and in humans Animal studies show that when administered simultaneously by the spinal route, a synergistic interaction occurs; however this interaction has not been demonstrated in humans The aim of the study was to evaluate a possible interaction between fentanyl (FN) and clonidine (CL), administered by the intramuscular (i.m.) and the epidural (e.p.) routes, in patients undergoing total hip replacement (THR).

Material & Methods: After institutional approval and informed consent, fifty ASA I–II patients scheduled for THR where randomly distributed into five groups that received 150 μg of FN and CL or saline (SS) by the following routes:

Group	I	II	III	IV	V
e p	SS	FN	CL	FN + CL	SS
i m	FN + CL	CL	FN	SS	SS

Study drugs were administered double blind before induction. Surgical anaesthesia was maintained with 60% N_2O in O_2, and Isoflurane (ISO) given at the required concentrations to maintain MAP and HR within 20% of baseline. We assessed: intraoperative ISO requirements (%, AUC), pain intensity (VAS) and sedation (Ramsay, SED) evaluated on arrival to recovery (VAS-RR) and at the time of analgesia request (VAS-TAR). Results were analyzed by ANOVA

Results & Discussion: All groups were comparable regarding demographic data, baseline MAP/HR, duration of surgery and degree of sedation Results are expressed as mean values (SD not shown)

GR	% ISO	ISO (AUC)	VAS-RR	TAR (min)	VAS-TAR
I	0.28	36	7.3	7	8.5
II	0.24	39	4.8	30	6.8
III	0.20	40	3.8	33	7.3
IV	0.14	24	1.3*	68*	7.3
V	0.92*	137*	4.8	23	8.1

ISO requirements were reduced in all groups (*$P < 0.05$) in relation to saline. Lowest ISO concentrations were required when FN and CL were given epidurally (Group IV), in the same group, VAS-RR was significantly lower (*$P < 0.05$) and the TAR prolonged (*$P < 0.05$) when compared to the rest of the groups

Conclusions: The simultaneous administration of 150 μg epidural FE and CL induces a reduction in ISO requirements and post-operative analgesia. The effects of the drugs seem to be additive (no interaction)

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A.390 Effects of clonidine on conductances active during post-tetanic hyperpolarization in peripheral nerve: studies of local anaesthetic action of clonidine

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Background: Coadministration of local anesthetics and Clonidine (Clo), an α2 adrenoceptor agonist, enhances the duration and intensity of peripheral nerve block (1). Clinical observations and in vitro studies suggest that the local anesthetic effect of Clo may be due to direct action on the C fibers (small, unmyelinated fibers responsible for pain transmission) In recent experiments, we showed that Clo increases and prolongs post-tetanic hyperpolarization (PTH), following a train of action potentials in peripheral nerve. This effect is reversible and dose-dependent at tested concentrations (EC50 = 20 μM) and could be mediated through α2-adrenoceptors (2). Such a prolongation of hyperpolarization limits the frequency of discharge by increasing the firing threshold and thus might contribute to the modulation of sensory input The present study was undertaken to determine the mechanisms by which Clo enhances PTH and thus affects peripheral impulse conduction

Methods: The effects of Clo on post-tetanic membrane potential were examined in the desheathed rabbit vagus nerve by the sucrose-gap method. The C-fiber monophasic compound action potentials were elicited by supramaximal stimulation and PTH was recorded after a train of action potentials (10 s, 15 Hz). Test solutions were applied for 20 min All experiments were carried out at room temperature

Results: Pharmacological studies show that Clo increases and prolongs PTH in a similar manner to potassium conductances blockers (Barium, Césium, TEA). These conductances are hyperpolarization-activated inward currents which short-circuit the major part of the hyperpolarization due to the hyperactivity of the Na+/K+ pump following tetanic stimulation (3)

Discussion and Conclusion: On the basis of these results, the hypothesis is that Clo may inhibit inwardly rectifying potassium channels. To characterize and study the effects of Clo on potassium conductances, the patch-clamp technique will be used on rat nodose ganglion and dorsal root ganglion neuron cell bodies. A better understanding of mechanisms by wich Clo interrupts impulse conduction in peripheral nerve may facilitate search for more specific pharmacological substances and may determine optimum drug combinations reproducing powerful analgesia with less side effects

Acknowledgements: Abbott AG, Astra Pharmaceutica AG, Boehringer Ingelheim, B. Braun Medical AG, FNRS 31-42404.94

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A.391 Effects and plasma concentrations of clonidine added to local anaesthetics for axillary plexus blocks

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Background and Goal of the Study: Clonidine (C) has been shown to enhance peripheral neural blockade when added to local anaesthetics, owing to a local action (1). However, a central analgesic effect due to blood absorption cannot be definitely excluded in the absence of pharmacokinetic study. This double-blind randomised study compared clinical effects and plasma concentrations of C added to local anaesthetics for axillary nerve block and those of C intramuscularly injected

Materials and Methods: After informed consent and institutional approval, 20 ASA-1 patients, scheduled for carpal tunnel repair, were studied. All axillary nerve blocks were performed by injection of lidocaine (200 mg) and bupivacaine (150 mg) after identifying the median nerve by a stimulator. C (150 mg) was given at random either with local anaesthetics (Group With; n = 10) or intramuscularly (Group IM; n = 10) To ensure that the study was double-blind, saline was injected intramuscularly in Group With. Sensory blocks using pinprick test in both ipsi- and controlateral upper limbs, blood pressure, heart rate, and sedation (from 0 = alert to 4 = comatose) were measured before and 20, 40, 60 and 120 min after injections. At these times, plasma C concentrations were measured by radioimmunoassay method (Bioscienta). Data were analysed by contingency table and ANOVA *P* was set at 0 05

Results and Discussion: Patients were sedated similarly in both groups. Haemodynamics were unchanged. C concentrations as well as sensory block intensity expressed as the ratio of ipsi- and controlateral pinprick scores were greater in Group With (Table).

Conclusion: Increased blood absorption of C may partly account for enhancement of the sensory block when C is added to local anaesthetics

	Before	20 min	40 min	60 min	120 min
C conc (ng/ml) *m* ± *SD*					
With	0	0 5 ± 0 1	0 7 ± 0 1	0 7 ± 0 1	0 7 ± 0 1
IM	0	0 4 ± 0 1	0 5 ± 0 1	0 5 ± 0 1*	0 7 ± 0 2
Sensory Score Ratio *m* ± *SD*					
With	1 0 ± 0 3	0 2 ± 0 2	0 1 ± 0 2	0 0 ± 0 0	0 0 ± 0 0
IM	1 0 ± 0 1	0 2 ± 0 2	0 1 ± 0 2	0 1 ± 0 1*	0 1 ± 0 1*
Sedation Score *median, range*					
With	0, 0–0	1, 0–3	1, 0–3	1, 0–3	1, 0–3
IM	0, 0–1	1, 0–2	2, 0–3,	1, 0–3	1, 0–3

* p ≤ 0 05 comparisons between groups

Acknowledgements: This work is supported by a grant from the Fondation de l'Avenir, Paris, France.

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A.392 Addition of nalbuphine to peribulbar anaesthesia: clinical usefulness?

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Background: The aim of this study was to compare analgesic effects, side effects and requirements for supplemental analgesic therapy after retinal detachment surgery performed under peribulbar anaesthesia, in patients given peribulbar (PB) or subcutaneous (SC) nalbuphine.

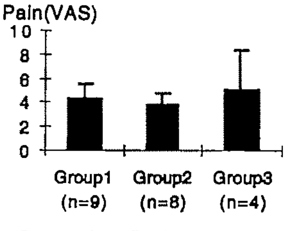
Methods: After institutional approval, in a randomized, double blind controlled trial, 98 patients each received two solutions with PB anaesthesia (2% lidocaine-0 5% bupivacaine) one PB and the other SC. Group 1 (n = 34) received 1 ml PB plus 1 ml SC of normal saline. Group 2 (n = 30) received 1 ml nalbuphine (10 mg) PB plus 1 ml SC of normal saline Group 3 (n = 34) received 1 ml PB of normal saline plus 1 ml SC of nalbuphine Pain was evaluated at the end of the surgery and 1, 2, 3, 4, 8, 12 and 24 h afterwards, using a linear visual analogue scale (VAS) from 0 (no pain) to 10 (the worst imaginable pain). Patients whose pain exceeded 3/10 received iv propacetamol 2 g every 6 h. IV ketoprofen was added every 8 hours if pain still exceeded 3/10. Side effects were recorded at each pain evaluation.

Results: The 3 groups were comparable in age, sex ratio, weight, surgical duration and type of procedure (scleral buckling and transscleral cryo) VAS pain rating were low in all groups. Only 22% patients had pain scores at 3/10 or above (figure) Duration of adequate analgesia did not differ between groups (table). All groups were comparable in analgesic requirements.

Duration of adequate analgesia (minutes)

	Group 1	Group 2	Group 3
Mean	189 ± 106	164 ± 93	251 ± 197
Range	50–337	63–276	85–537

mean ± SD, NS



Conclusion: Peribulbar anaesthesia provided adequate postoperative pain relief after retinal detachment surgery. The results of this study suggest that addition of nalbuphine to local anaesthesia does not improve postoperative analgesia.

A.393 Does systemic verapamil potentiate spinal anaesthesia?

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Background & Goal of Study: It has been experimentally shown that intrathecal administration of calcium channel blocker and local anaesthetic combination produces more potent sensory and motor blockade (1) However, the effects of systemically administered calcium channel blockers on spinal anaesthesia are unknown. We aimed to assess whether systemic administration of verapamil potentiates spinal anaesthesia

Materials & Methods: In order to avoid possible deep hypotension, only patients who would have been planned saddle blockade were selected. 20 ASA class I or II adult patients, were randomly divided into two equal groups Verapamil of 5 mg or saline (C) of 1 ml as control was given intravenously 30 minutes before the blockade, and then spinal saddle blockade was performed using 2 ml bupivacaine of 0.5%. Sensory blockade was assessed with Pin-prick test, and voluntary control of anal sphincter was used to assess motor blockade. The times (T) from the intrathecal administration of bupivacaine to the beginning (B), completion (C) and resolution (R) of sensory (S) and motor (M) blockade were measured. Arterial blood pressures and heart rates were monitored. Student's t and Chi-square tests were used for statistical analysis Data are expressed as mean ± standard error $P < 0\ 05$ was considered significant

Results & Discussion: Both groups were comparable for demographic data. There were no statistically significant differences between the two groups for the times about blockade shown in table. Arterial blood pressure was lower in verapamil group when compared with control group at 30th min ($P < 0.05$)

	T-BS (sec)	T-BM (sec)	T-CS (sec)	T-CM (sec)	T-RS (min)	T-RM (min)
V	78 ± 19	126 ± 32	169 ± 70	204 ± 53	216 ± 25	229 ± 52
C	46 ± 12	61 ± 14	113 ± 55	158 ± 81	180 ± 18	263 ± 35

No potentialization of spinal anaesthesia in our study may be explained with the assumption the dose of verapamil can not produce enough concentrations required for interaction with local anaesthetic in spinal cord

Conclusion: We concluded that the systemic administration of 5 mg verapamil does not potentiate spinal anaesthesia.

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A.394 A comparison between subarachnoid administration of bupivacaine 0.5%, mepivacaine 2% and prilocaine 5% based on a pharmacodynamic model

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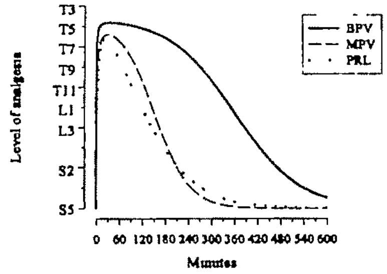
Background and Goal of the Study: A mathematical model for the analgesic effect of subarachnoidally administered 0 5% Bupivacaine (BPV), has been recently described[1]. Using the same structural model, we wanted to estimate the parameters for 2% Mepivacaine (MPV) and 5% Prilocaine (PRL), and compare it to BPV

Materials and Methods: 37 adult consenting patients were enrolled in the study and assigned to receive either MPV (28) or PRL (9) The anesthetic was injected via a Withacre 25G spinal needle at L3–L4 level in the sitting position Doses ranged from 70 to 92 mg (MPV) and 65 to 90 mg (PRL) The level of blockade was measured periodically (pinprick) until analgesia dissipated enough as to enable complete movement of both legs Nonlinear mixed effects modeling (NONMEM) was used to estimate the parameters of the model and the variability (inter and intra individual) for MPV and PRL Based on this predictions, onset time (time to reach T10), duration (time above T10) and offset time (time from Emax to L1) were calculated and compared to BPV[1].

Results: The graph shows the time course of effect for BPV (12 mg dose), MPV (80 mg), PRL (80 mg), according to the model predictions. Relevant end points based on typical values are reported on the table



	BPV	MPV	PRL
Onset (min)	1	4	7
Duration (min)	272	112	58
Offset (min)	294	114	78

Conclusion: Based on model predictions, PRL had a significantly shorter duration and a faster offset. Estimates of interindividual variability around the parameters of the model were important in the case of PRL, probably due to the small number of individuals Further studies should be needed to corroborate these results.

References

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A.395 A pharmacodynamic model for the effect of subarachnoid injection of bupivacaine 0.5%: prospective validation

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Background and Goal of the Study: The use of mathematical models to describe the relations between drug administration and effect, enables us to elaborate predictions of expected effect, in slightly different clinical scenarios. After a model is constructed, it is convenient to validate it prospectively in a different population Our goal was to validate the following model by Schnider et al[1]

$$L_p = E_m \times \frac{\text{Dose} \times (e^{-\alpha_1 t} - e^{-\alpha_2 t})}{F + \text{Dose} \times (e^{-\alpha_1 t} - e^{-\alpha_2 t})}$$

where L_p stands for the level predicted, E_m for the maximal level, α_1 and α_2 are the rate constants for onset and offset of effect and F is a scaling factor, to characterize the relation between subarachnoidally injected 0 5% plain Bupivacaine (BPV) and the effect considered as the level of blockade achieved.

Materials and Methods: 12 adult consenting patients were enrolled in the study. 0 5% BPV was injected subarachnoidally via a Withacre 25G spinal needle at L_3–L_4 level in the sitting position The dose ranged from 10 to 15 mg The level of blockade was measured periodically (pinprick) until analgesia dissipated enough as to enable complete movement of both legs. Nonlinear mixed effects modeling (with NONMEM) was used to estimate the robustness of the model in describing our observations

Results and Discussion: The parameters that we estimated based on our data are reported in the table and compared to the originally described by Schnider et al[1]

	α1 (min^{-1})	α2 (min^{-1})	F	Emax
Gambús	0 015 (18)	0 053 (23)	0 86 (43)	T4 (0 4)
Schnider	0 012 (8)	0 0608 (16)	0 22 (23)	T4 (2 1)

reported as values (%CV) An empirical bayesian estimation with the model and parameters from Schnider et al[1], was able to predict our observations adequately

Conclusions: An estimated median absolute prediction error (MDAPE) of 5 2% demonstrates good accuracy of the model in describing our observations Differences were detected around the scaling factor F, perhaps due to the small number of individuals in our population (12) compared to the original description of the model (96). This model can be used to predict analgesic effect after spinal administration of 0 5% BPV

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A.396 Unilateral spinal anaesthesia: effects of speed of intrathecal injection

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Background: It is currently believed that rapid injection of the local anaesthetic solution during unilateral spinal anaesthesia causes turbulence that could modify its distribution into the spinal canal The aim of this randomized, double-blind study was to evaluate whether the speed of intrathecal injection affects lateral distribution of spinal block

Methods: With Ethic Committee approval and patient consent, spinal anaesthesia was performed by 8 mg of 0 5% hyperbaric bupivacaine in 30 patients scheduled for unilateral leg surgery Dural puncture was performed by 25-gauge Whitacre spinal needle (Becton-Dickinson, N J , USA). After free flow of cerebrospinal fluid was observed, the needle bevel was turned toward dependent side of spinal canal, then patients were randomized to receive anaesthetic solution injected over 80 sec (SLOW, n = 15) or 6 sec (FAST, n = 15) Lateral position was maintained for 15 min with the side to be operated upon dependent The presence of an adequate sensory (above L_1) and motor (3°) blocks on surgical side, without one or both modalities on non-surgical side, or sensory and motor blocks lasting 20% longer on operated than non-operated side was defined as successful unilateral spinal anaesthesia Mann-Whitney test and Fisher exact test were used as indicated A value of $P < 0.05$ was considered as significant

Results: The two groups were comparable concerning anthropometric data and haemodynamic changes. Main results are presented in the table

	Slow (n = 15)	Fast (n = 15)
Unilateral sensory block	13 (86%)	8 (53)
Unilateral motor block	13 (86%)	10 (66%)

No significant differences in lateral distribution of spinal block were observed between the two groups. No differences in the number of patients showing sensory and motor blocks 20% longer on operated than on non-operated side were observed between the two groups.

Conclusion: Our results demonstrated that speed of intrathecal injection does not affect preferential distribution of 8 mg of 0.5% hyperbaric bupivacaine towards the operated side when a Whitacre spinal needle is used.

A.397 Continuous spinal anaesthesia with catheter over the needle: preliminary report

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Background and Aims: Continuous spinal anaesthesia (CSA) using small gauge catheters is still a matter of debate, cauda equina syndrome being the most feared complication This study was designed to evaluate a new 24G spinal catheter threaded over a 27G Quincke spinal needle (Spinocath® B. Braun Medical Division)

Methods: After IRB approval and written patient consent, 14 ASA 1 or 2 patients scheduled for elective surgery of lower limbs or low abdominal region were studied. Catheter insertions were all made in a sitting position using a median approach at L2–L3 level. After epidural placement of the introducer, the 27G Quincke spinal with the "over the needle" 24G spinal catheter was introduced until the dural click was felt and free flow of CSF in the catheter was obtained. The wired 27G spinal needle was then removed and the 24G spinal catheter was threaded 3 cm into the subarachnoid space. 7.5 mg isobaric 0.375% bupivacaine was injected as initial dose and 3.75 mg increments were used in order to achieve a Th 10 sensory block level with a maximum of 15 mg We studied ease of insertion (dural click sensation, flow of CSF through the spinal catheter) We recorded frequency of catheter induced paraesthesia and we measured the efficiency of the first initial dose as well as the need of additional ones in order to achieve a sensory block level at Th10. We recorded presence of PDPH and neurological exams were performed the day after surgery

Results: Mean age was 64 years, mean weight was 81 Kg and mean height was 170 cm. Dural click was felt in 12 patients. CSF flow was obtained in 12 patients at first attempt within 5 seconds and, in 1 patient, three attempts were needed to thread the catheter up. Subarachnoid placement of the catheter was impossible in 2 patients. We recorded 80% catheter induced paraesthesia. Initial dose was efficient in 7 patients and a median sensory block level of Th4 was obtained. 2 patients required 1 top up in order to achieve a sensory block level above Th 10; median sensory block levels before top up were at L1 and at Th3 after. 2 patients needed 2 top ups (maximum dose); median sensory block levels before first top up were at L3, at L2 before the second and at Th7 after the second top up. 1 patient, despite maximum dose, kept to a level of Th12 No PDPH were recorded and neurological exams remained normal

Conclusions: Initial dose, when efficient, gave too high sensory block levels. The need of top ups is probably related to malposition of the spinal catheters. The catheter used is not predictable enough in the way it has been utilised in our study.

A.398 Continuous spinal anaesthesia: is there a risk of infection?

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Background and Goal of Study: The major benefit of continuous spinal anaesthesia (CSA) compared to single-shot spinal anaesthesia is that it allows subsequent injection of local anaesthetics. Moreover, it enables postoperative pain therapy. Potential risks of this method are lesions of nerves and/or vessels as well as infection. This study will contribute to research on the risk of infection.

Materials and Methods: In 144 patients (51 m/93 f) undergoing lower limb surgery, and who successfully underwent CSA, cerebrospinal fluid (CSF) was sampled both immediately after positioning and before removing the catheter. Leukocytes, proteins and glucose concentration were determined Meningism and infection parameters such as leukocytes in blood, CRP, ESR, temperature, skin lesions at the insertion site, were compared preoperatively and by removal. The catheter was removed under rigorous aseptic conditions. The tip was cut and washed with saline. CSF, tip and saline were cultured to establish whether there was microbiological contamination.

Results and Discussion: In 126 (87.5%) patients, all parameters could be determined. Leukocytes, proteins and glucose concentration in CSF did not change significantly. In five cases (3.9%), bacteria were found in CSF. The catheter tip was contaminated in eight cases (9.4%), and saline in one (0.8%) Staphylococcus epidermidis was the most frequently cultured microorganism. There is a statistically significant positive correlation (= 0.25) with the indwelling catheter time. Signs of local inflammation (erythema) at the insertion site appeared in three out of 24 cases (12.5%) with CSA lasting longer than 90 h Therefore, the catheter had to be removed. However, no patient showed evidence of local or systemic infection with CSA for up to 195.5 h.

Conclusions: CSA is a safe method in respect of infection risk, if it is used for up to 200 h An absolutely meticulous technique of insertion and handling the catheter is mandatory, as well as a daily inspection of local inflammation at the site of insertion

A.399 Respiratory muscle strength after spinal anaesthesia

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Background & Goal of Study: Spinal anaesthesia can produce motor block of the thoracic nerve roots and may therefore reduce both inspiratory and expiratory muscle strength. Measurements of peak inspiratory and expiratory flow have implied that weakness of these muscle groups occurs, however this has not been quantified by respiratory muscle assessment We therefore aimed to determine the relative reductions in both inspiratory and expiratory muscle strength following spinal anaesthesia.

Materials & Methods: 13 consecutive patients undergoing lower limb or urological surgery consented to take part in the study. Maximal inspiratory and expiratory mouth pressures (MIP, MEP) were measured preoperatively and at intervals during and after surgery using a PK Morgan Pmax monitor These tests rely on patient effort. To gauge the consistency of effort we asked patients to perform maximum hand grip manoeuvres with the nondominant hand, using a Jamar hand-grip dynamometer. A reduction in grip strength coinciding with a block level below T1 would suggest a reduction in volitional patient effort and suggest that corresponding respiratory efforts were also submaximal, allowing their exclusion. Patients received 2.5–3.0 mls 0.5% heavy bupivacaine and all measurements were made supine To reduce the effect of learning all measurements were recorded a minimum of 8 times before surgery. Data is presented as a percentage of the average of the 3 best preoperative measurements

Results & Discussion:

Time mins	Mean MIP	SD	Mean MEP	SD	Mean Grip	SD	Mean block level	SD
Pre	100		100		100		nil	
10	96	14	71	31	95	8	T7	2
30	92	15	66	27	95	10	T5	2
60	87	15	69	28	93	12	T6	2
90	89	14	73	26	96	9	T7	3
120	94	14	77	25	98	11	T9	3
150	93	12	81	26	97	14	T11	3
180	97	9	87	27	100	10	T12	2

We found that inspiratory muscle strength was only mildly affected however expiratory muscle strength was reduced to a maximum of 66% of preoperative values and had not fully recovered 3 hours after the commencement of the block.

Conclusion: We conclude that inspiratory muscle strength is little affected following spinal anaesthesia, however expiratory muscle strength is reduced and this is likely to reduce the patients ability to cough

A.400 A comparative efficacy study of hyperbaric lidocaine 1.5% and mepivacaine 2% for spinal anaesthesia

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Background: Recently, the safety of lidocaine as a spinal anesthetic has been questioned(1). Some have advocated using lower concentrations of lidocaine for spinal anesthesia(2).

Mepivicaine has been used in the past as a spinal anesthetic, but its popularity waned because of its longer duration of action especially at higher concentration(3). This study compares hyperbaric 2% mepivicaine with 1.5% lidocaine with regard to the onset, duration and quality of the subsequent motor and sensory block.

Methods: After obtaining IRB approval and informed consent, 35 ASA class 1–2 adult male/female patients about to undergo lower extremity, lower abdominal or genitourinary surgery were placed into one of two groups based on the anesthetic solution received. group 1 patients received 75 mg of a 2% mepivicaine in dextrose 3 3% in water (3.75 ml) and group 2 received 1.5% lidocaine in dextrose 7 5% in water (5 ml). Before placing the spinal solution all patients were prehydrated with 500 ml lactated Ringers solution and had standard monitors placed. The spinal solution was injected at a rate of 5 ml/sec while the patients were in the sitting position Following injection of the spinal anesthetic, patients were placed in the supine position and all measurements were taken by an anesthesiologist that was blinded to the anesthetic agent used. The onset degree and duration of sensory block was assessed by the patients response to pinprick and a modified bromage scale was used to assess the onset, degree and duration of motor blockade Results are expressed as the mean + SEM.

Results:

	1 5% lidocaine n = 19	2% mepivicaine n = 16
Time to maximum sensory level (min)	10 ± 1	10 ± 1
* Highest Dermatomal level (Thoracic) plus range	4 (6–2)	5 (8–2)
* Complete sensory recovery (min)	172 ± 22	242 ± 39
Time to maximum motor block (min)	7 ± 4	7 ± 3
* Complete motor recovery (min)	126 ± 23	203 ± 44

* Denotes $p < 0\ 05$

No patients experienced transient radiuclar irradiation.

Conclusion: From the initial results, hyperbaric 2% mepivicaine appears as clinically efficacious as lidocaine 1.5% for spinal anesthesia With regard to recovery from sensory and motor blockade, mepivicaine 2% requires significantly more time for complete recovery than does lidocaine

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A.401 Influence of spread of hyperbaric spinal anaesthesia on quality and duration of spinal block

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Background and Goal of Study: According to Greene (1) local anesthetics (LA) are eliminated from the subarachnoid space by vascular absorption and diffusion across arachnoid and dura membranes. Theoretically, with a larger surface of diffusion and absorption, elimination of LA should be faster. Thus, if significantly different anesthetic levels are obtained with same dose of LA, elimination of LA in patients with higher levels should be accelerated. This phenomenon might be clinically evidenced by faster regression and shorter duration of spinal anesthesia. The present study was designed to evaluate this hypothesis

Methods: After institutional approval and individual informed consent, 40 ASA I-II patients scheduled for lower limb surgery under spinal anesthesia, were studied 3 ml (15 mg) of hyperbaric bupivacaine 0 5% were injected intrathecally with the patient in sitting position. After LA injection, in order to obtain significantly different anesthetic levels, the patients were randomly placed either in a horizontal or in a 30° elevated torso position, and remained in these positions until the end of the study period Sensory level and motor block were evaluated by patient's perception of cold (ether) and the Bromage scale every 15 min. until regression to L4 and/or total motor recovery. Appearance of pain at operative site was noted Results are expressed as mean ± SD or median (ranges) and were analysed using Mann-Whitney or unpaired Student-t test as required

Results: The main data are summarized on the following table.

	Horizontal (n = 20)	30° elevated torso (n = 20)
Max sensory level	T 3 5 (T1–T9)	T10 (T6–L1)**
Regr of 2 segm (min)	110 ± 30	159 ± 49**
Regr. to L4 (min)	269 ± 53	336 ± 58**
Max. motor block	4	4 (2–4) NS
Total mot recovery (min)	173 ± 34	233 ± 56**
Pain at op site (min)	220 ± 68	270 ± 56*

*$p < 0\ 05$ **$p < 0\ 005$

Conclusion: These results support our hypothesis: with identical doses of LA, duration of anesthesia was significantly longer in patients presenting lower anesthetic levels (smaller surface of LA elimination) indicating slower absorption and diffusion of LA from subarachnoid space.

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A.402 Combined spinal/epidural anaesthesia. A prospective clinical comparison between the needle-through-needle and the double-segment techniques

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Background: We conducted a prospective, randomized, blind study in order to compare the double-segment and the needle-through-needle techniques for combined spinal/epidural anesthesia (CSE)

Methods: With ethical committee approval and patient's consent, 90 patients receiving CSE for elective orthopedic and urologic surgery were randomized to receive CSE using the needle-through-needle techniques (SST, n = 45) by means of the "adjustable Durasafe®" spinal needle (Becton Dickinson, N J., USA), or the double-segment technique (DST, n = 45) All patients received intrathecal injection of 15 mg of 0 5% plain bupivacaine Impossible location of intrathecal space was recorded An observer blinded to CSE technique measured the time required from skin disinfection to achieving a sensory block up to T_{10} (pinprick) and the need for epidural top-up before surgery. The day after surgery patients were checked for neurologic complications, while acceptance of anaesthetic procedure was evaluated on a 2 point scale 1) good, I can repeat it if necessary, 2) bad, I would prefer a different technique if necessary Unpaired t-test and chi-square test were used as indicated A value of $P < 0.05$ was considered as significant

Results: Anthropometric data were similar in the two groups No neurologic complications were observed in both groups The tip-to-tip distance between spinal and Tuohy needle measured in the SST group at the end of anaesthetic procedure was 7.0 (range 2 1–15.0) mm Main results are shown in the table

	SST	DST
Anest Procedure (min)	23 5 ± 11	29 8 ± 8 9$
Failed dural penetration	3 (6 6%)	1 (2 2%)
Epidural top-up	5 (11%)	4 (8 8%)
Acceptance Good/Bad	40/5	29/16$

$$P < 0\ 01$ vs SST

Conclusions: The present study demonstrated that the needle-through-needle CSE allows a similar rate of successful spinal block, but is faster and better accepted by patients when compared to the sequential puncture. Spinal needle employed in SST group was fixed to the hub of Tuohy needle and protruded up to 15 mm beyond the tip of Tuohy needle: this may explain the low failure of dural puncture as compared to previous studies (1, 2).

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A.403 Epidural anaesthesia reduces haemodynamic response to carbon dioxide insufflation during laparoscopic cholecystectomy

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Background and Goal of the Study: Peritoneal insufflation of CO_2 during laparoscopic cholecystectomy induces major hemodynamic changes characterized by an increase in mean arterial pressure and a decrease of cardiac index (1)

We investigated the effects of thoracic epidural anaesthesia compared to general anaesthesia on haemodynamic alterations during laparoscopic cholecystectomy

Materials and Methods: Twenty ASA I-II patients scheduled for laparoscopic cholecystectomy were randomised to receive general anaesthesia with controlled ventilation followed by IM pethidine administration 50–100 mg for postoperative analgesia (G group) or thoracic epidural 2% lignocaine with Adrenaline 1/200000 and Fentanyl 1 μg/kg intraoperatively with spontaneous ventilation (block T4-L2) supplemented with Midazolam and Fentanyl iv followed by continuous epidural 1% lignocaine with Fentanyl 2 μg/ml 5 ml/h with PCA of 2 ml boluses at 15 min interval 24 h postoperatively (E group) We monitored for both groups mean arterial pressure (MAP), heart rate (HR), $ETCO_2$ and SaO_2 before the induction of anaesthesia (1), after induction of anaesthesia (2), 2 min after anti-Trendelenburg 30° (3), 5 (4), 10 (%), 15 (6) min after peritoneal insufflation and 2 min after CO2 exsufflation (7). Statistical analysis was performed using Mann-Whitney U test and Wilcoxon signed ranks test

Results: Patient characteristics and duration of surgery did not differ between groups. MAP decreased significantly in group G after the induction of anaesthesia and decreased further after tilting to head-up position ($p < 0\ 01$) followed by a significant increase after peritoneal insufflation (p <

0.01). Heart rate decreased significantly only in the E group after induction and tilting into head-up position being significantly lower compared to the preinduction value ($p < 0.05$).

Conclusion: Thoracic epidural anaesthesia prevents MAP increase after peritoneal insufflation with CO_2 during laparoscopic cholecystectomy

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A.404 Epidural pneumocephalus after epidural lumbar technique

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Background and Goal of Study: We describe and discuss the physiopathology about an epidural pnemocephalus (PN) after the "loss-of-resistance" technique using an air filled syringe for identification of the epidural space.

Materials and Methods: A male patient, 76 years old, scheduled for prostatical adenomectomy Puncture and placement of an epidural catheter by loss-of-resistance with gassy plunger (Penfix 421 Braun, Germany) with the patient in sitting position. After locating the epidural space the patient felt something unpleasant like "something that ran up all over the back till the head" and pulsation pain on the temple. The Brain Tomography (BT) showed ectopical air placed in pretemporal and prefrontal spaces.

Results and discussion: The epidural space has been classically described like a space which finished at its top side at the level of the foramen magnum The critical point from the air cross from its situation in cervical epidural level to cranium epidural space, is at level of odontoid process level. The BT from this patient showed up the air passing between the duramater and the odontoid ligament. The individual variations in the composition of the epidural space could explain this particular crossing of air.

Conclusion: The epidural location from a PN after making a lumbar epidural technique is a new complication that has not been described until now. It will be necessary to do a prospective study to confirm these datum from the anatomical hypothesis about the etiopathogeny, and verify the real rate of this complication.

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A.405 Jet injector compared with needle and syringe for administration of local anaesthetic

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Background and Goal of Study: Jet injector systems (JIS), which use a high velocity jet of liquid to pierce the skin, were initially developed in the 1930s Little data exists comparing the efficacy of JISs with a conventional needle and syringe (NS) in delivering local anesthetic agents. This study compared the local anesthetic requirement and serum anesthetic levels of lidocaine using a JIS and a conventional NS

Materials and Methods: Following IRB approval, 30 consenting adults scheduled for elective cardiac catheterization were randomized to either the NS group (control) or JIS group. The NS group (n = 15) received 2% plain lidocaine, and the JIS group (n = 15) received a single injection (Medi-Ject Corp, Medi-Jector II) of 1 ml of 1% plain lidocaine prior to femoral cannula placement Both groups received additional 2% lidocaine from a NS, as needed for break-through pain during cannula placement. The serum lidocaine level of each patient was measured at baseline, after cannula placement, and 15 and 30 min after injection A visual analogue scale (VAS) score of the discomfort was obtained from each subject in the JIS group immediately following the injection.

Results and Discussion: The JIS subjects received significantly less lidocaine than the NS subjects (57 ± 65 mg vs 341 ± 71 mg, respectively [mean ± SD, unpaired t-test, $p < 0.001$]). The JIS did not cause significant discomfort (1.6 ± 1.7 VAS, range 0 to 5), and was reported as painless by 40% of subjects Serum lidocaine levels (μg/ml) are reported at times after injection in table

	At cannula placement	At 15 minutes	At 30 minutes
NS (n = 15)	5.4 ± 2.4	4.3 ± 1.6	5.3 ± 1.9
JIS (n = 13)	1.2 ± 0.7†	0.6 ± 0.2†	0.8 ± 0.2†

Therapeutic serum lidocaine levels are from 1–5 with >7 considered toxic. † Compared to mean NS at same time, $p < 0.05$ Data expressed as mean ± SEM for number of patients

Group means compared with one-way analysis of variance followed by Dunn's pairwise testing

Conclusion: The JIS compared to NS decreased the amount of lidocaine required for patient comfort during femoral cannula placement and resulted in lower serum lidocaine levels

This study was supported by a grant from the Baxter Healthcare Corporation.

A.406 The usefulness of colour Doppler ultrasound guided infraclavicular brachial plexus block

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Back ground & Goal of Study: The ultrasonography-guided nerve block has made possible to visualize the major anatomical structures (1)–(2) The aim of this clinical study was to estimate the usefulness of the color Doppler ultrasonography (CDUS)-guided modified infraclavicular brachial plexus block (m-IcBPB) (3).

Methods: After informed consent, 7 patients with persistent upper extremity pain participated in this study of the 37 CDUS-guided m-IcBPBs. The patient was placed in supine position and the arms were placed at the side Ultrasonographic examinations of the infraclavicular vessels and coracoid process were done using the linear probe (PLF-805 ST, PLF-703 ST/NT, 7.5 MHz. ECCOCEECX-SSA-340 ATM; TOSIBA, Japan) The scanning head was positioned inferior to the clavicle. The anatomic situation of the high axilla was recorded on a color printer (Tosiba TCP7700 TM; TOSIBA, Japan) After visualization of the anatomy, with the index finger palpating the coracoid process, the needle (23G–25 mm) syringe assembly was introduced medial to the coracoid process & advanced posteriorly, slightly cranially until the decreased resistance with penetration of the fascia clavipectoralis was felt on the plunger. After the thermic stimulation induced paresthesia in forearm was elicited (3), 1% mepivacaine (0.2–0.3 ml/kg) was injected Cutaneous current perception thresholds (CPT) were measured on the 2nd finger tip with neurometer (Neurometer-CPT Neurotron) before and after the m-IcBPBs.

Results: None of the patients showed hematoma, clinical symptoms of pneumothorax or needle induced neurological sequelae after the blocks. Two of the 7 patients had complete resolution of the persistent pain (CRPS) and 3/7 patients had a VAS of 5–3/10 following a series of m-IcBPBs. The mean CPTs with 5-Hz and 250-Hz stimulation were increased to greater than baseline 15 min after the m-IcBPB

Conclusion: Although further investigation is required, this clinical study suggests that the CDUS-guided m-IcBPB is easier than the method using B-mode ultrasonography, and prevents the complications and could increase the success rate of the blocks in obese patients.

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A.407 Flow cytometric analysis of *in vitro* effect of bupivacaine on platelet activation

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Background & Goal: Extradural anaesthesia with bupivacaine reduces post-operative venous and arterial thrombosis. In addition to haemodilution, increasec lower limb blood flow and changes in fibrinolysis, the membrane stabilising and anti-leukocyte adherence effects of amide local anaesthetics which reduce platelet activation may also be important. Platelet aggregation studies show bupivacaine reduces aggregation but only at toxic doses. (1) Peak plasma concentrations 15–30 min after extradural anaesthesia are 1–2 μg/ml, toxic values are 4 μg/ml. Aggregation studies require the preparation of platelet rich plasma, but flow cytometry may be a more sensitive measure of early changes in activation. A whole blood method has been described in which fluorescent antibodies are used to label platelet membrane proteins. (2) Early activation is marked by a conformational change in the GPIIb-IIIa surface protein complex and can be measured using a polyclonal anti-fibrinogen antibody which binds to fibrinogen on the receptor surface After degranulation proteins from the alpha and lysosomal granules are expressed on the platelet surface and can be measured using CD62 and CD63 antibodies respectively.

Materials and Methods: Blood from 8 fit medication free volunteers was drawn without stasis into 1/10 volume 3.8% trisodium citrate and either labelled and analysed at once for a baseline value, or incubated at 37°C for 1 h with saline, 0.4, 2 or 10 μg/ml bupivacaine before labelling and analysis. The number of activated platelets out of a count of 5,000 was measured.

Results and Conclusions: Results were analysed using the Wilcoxon signed rank test. Samples labelled with the anti-fibrinogen antibody showed a significant increase in activation when incubated with saline compared with baseline (p = 0.01) Incubation with 0.4 μg/ml bupivacaine elicited a non significant decrease in activation, but incubation with 2 and 10 μg/ml resulted in significantly reduced activation, (p = 0.05). There was no significant change in activation under any of the study conditions using the CD62 and CD63 antibodies Bupivacaine at concentrations found after extradural anaesthesia decreases early platelet activation, but does not alter degranulation

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A.408 The electroencephalographic effects of spinal anaesthesia

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Background and Goal of Study: During surgery, the electroencephalographic (EEG) features of combined regional (RA)/general (GA) anaesthesia differ from those of GA alone [1] To investigate the independent effects of sensory blockade, we compared EEG variables and sedation scores from patients having spinal anaesthesia (SA) with those occurring over time in a control group.

Materials and Methods: 17 patients, aged 18-65, undergoing elective surgery were studied preoperatively An SA group (n = 8) was compared with a control group (n = 9). Median frequency (MF), 95% spectral edge frequency (SEF), bispectral index (BIS) and relative percentage power in EEG frequency bands (delta 0–3.75, theta: 4 0–7.75, alpha· 8.0–13.5, beta: >13 75 Hz) were recorded continuously from frontotemporal electrodes with an Aspect A-1000 EEG monitor. Data were downloaded to a computer for later analysis Sedation scores[2] were recorded every 5 minutes. Data were collected for 30 min (S1). SA patients then received 3 ml intrathecal bupivacaine 0.5%. Hypotension was treated with fluid. 30 min after the end of S1, data collection was recommenced for 30 min (S2) Median sedation scores and mean EEG values were calculated in each patient for S1 and S2 Median group sedation scores were compared by Wilcoxon rank-sum or signed-ranks tests, mean group EEG data by t tests, paired and unpaired.

Results and Discussion: Sedation scores did not change with time or SA EEG data is shown below (mean (SD)).

	Control group (n = 9)		SA group (n = 8)	
	S1	S2	S1	S2
SEF Hz	17 6 (5 6)	17 5 (4 9)	18 1 (5 5)	23 4 (2.9)*†
MF Hz	4.0 (2 1)	3 9 (1 7)	3 9 (1.6)	6 3 (3 6)*†
BIS	92 6 (4.1)	92 7 (3 5)	92 6 (3 5)	96 2 (1 3)*†
alpha%	13 4 (8 6)	14 2 (8 4)	14 2 (9 3)	15 1 (8 2)
beta%	12 3 (8 0)	11 7 (6.2)	12 2 (6 4)	24 5 (13 9)*†
theta%	16 8 (4 4)	15 3 (4.2)*	16 0 (3 0)	13 9 (3 9)
delta%	57 5 (15 8)	58 9 (14 7)	57 7 (14 9)	46 5 (14 3)*†

Significant differences at $p < 0$ 05· * within group between S1 and S2, †· between groups for S2

Conclusion(s): SA does not affect sedation scores. EEG changes differ from those occurring over time. Their contribution to EEG effects of combined RA/GA is unclear.

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A.409 Thoracic epidural anaesthesia and GUT mucosal perfusion assessed by gastric tonometry and laser Doppler flowmetry in coronary artery surgery

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Objectives: To assess the effect of thoracic epidural anaesthesia in patients undergoing coronary artery surgery on gastric intramucosal pHi during surgery and in the first 8 hours postoperatively and to see how this varies in comparison to blood flow measured using laser doppler flowmetry techniques.

Methods: 30 patients undergoing routine surgery were randomised prospectively to either receive thoracic epidural anaesthesia with bupivacaine and clonidine in conjunction with GA or GA alone. pHi was measured continuously using the Tonocap (Tonometrics, Finland) and recorded at 9 time points. Serum lactate was measured at 4 time points during the study period Laser Doppler flux was measured continuously (Moor Instruments, UK)

Results: The groups were well matched in terms of demographic and operative data. There was no significant difference between the two groups in pHi during the study period. However, pHi fell during bypass compared to prebypass levels and mean values of less than 7 3 were recorded in both groups Serum lactate was significantly raised in the non-epidural group 8 hrs post admission to ITU (p = 0.047). CO2 gap was significantly worse in the epidural group at 8 hrs post ITU. We found no significant difference between standard pHi and pH gap between the two groups. There were no deaths or major complications in either group. Laser doppler flux measurements initially fell at the start of bypass in both groups but then increased during rewarming and into the postoperative period indicating increased mucosal blood flow.

Discussion: TEA does not appear to alter the gastric mucosal perfusion as measured by tonometry or laser doppler flowmetry in this group of patients However, the number of patients studied were small and trends between the two groups may become significant if larger numbers of patients were studied pHi worsened in both groups to levels which have been previously described as critical, during and after the bypass period pHi is an indirect measure of gut blood flow and the changes in mucosal blood flow seen with the Laser Doppler Flowmetry technique suggest an increase in perfusion during rewarming and in the postoperative period This was not associated with improved pHi and may be due to either 1) an inappropriate redistribution of blood at the mucosal level 2) the development of an oxygen debt during the period of hypothermia on bypass which remains in the postoperative period despite the increase in mucosal blood flow

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A.410 Comparison of two anaesthetic procedures for removal of angioplasty introducers

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Background: Removal of femoral introducers used in PTCA (Percutaneus Transluminal Coronary Angioplasty) is seldom accompanied by bradyarrhythmias (that require atropine administration), important nuisances in the compression area and even angina We want to investigate if there are differences in hemodynamics, occurrence of arrhythmias, use of antiarrhythmic drugs and patient's comfort during introducers removal using two different anaesthetic procedures· femoral nerve blockade and local infiltration of the area

Material & methods: Following Ethics Committee approval 29 consenting patients submitted to scheduled PTCA were randomly enrolled and divided into two groups The femoral nerve blockade was the anaesthetic technique employed in 17 patients. This is a common procedure for knee arthroscopy (1) or surgery of fractured shaft of femur (2). The nerve was located with a peripheral nerve stimulator using a standard intensity of 2 5 mA. After the localization 25 ml of 1% lidocaine solution were injected, and introducers were removed 30 minutes later In the local infiltration group, 15 ml of 1% lidocaine were injected subcutaneously around the introducers. We studied distribution and quality of the blockade, occurrence of arrhythmias, necessity of antiarrhythmics, ischemic events, blood pressure (BP) and heart rate (HR) (basal and every minute after the removal) and degree of the patient's comfort. Statistical tests included t Student, Chi square and U Mann-Whitney

Results: Both groups were similar in age and sex distribution. Only four patients had arrhythmias (two in each group): three bradyarrhythmias (two of them requiring atropine) and the other premature ventricular contraction. No patient had angor. There were not statistically significant differences between both groups in any of the variables analyzed.

Discussion: Based on these results, both procedures can be chosen indistinctly, although the simplicity and brevity of the local infiltration probably makes it the elective anaesthetic technique for removal of PTCA introducers.

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A.411 Subarachnoid block and computerized sedation: haemodynamic profile

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Goal: To assess whether a computerized infusion with propofol achieves reliable sedation with stable hemodynamics.

Patients and Methods: Forty premedicated patients undergoing scheduled surgery under a subarachnoid block were randomly ascribed to two groups no sedation and target controlled infusion (TCI-Diprifusor®). Both groups matched for age (41 ± 16), height (169 ± 9), weight (72 ± 13) bupivacaine dosage (13 ± 2), and ASA. (Median ± standard deviation) No inotropics were required Heart rate, noninvasive blood pressure, S_pO_2 and ET CO_2 were recorded at baseline, after the block, at incision and at the end. Informed consent was obtained. Statistics: t-test Linear regression

Results: An observer's assessment of alertness/sedation[2] not higher than 3 was achieved with predicted plasma propofol median concentrations 1 4 μg/ml with a range of 0.6–2.9[1] in TCI group with a median of 3.2 changes/patient. No statistical differences in blood pressure were found between baseline values and throughout the procedure, nor between groups but heart rate was lower whilst on propofol. Blood pressure at the incision correlated closely with the final measurement in non-sedated patients (r = 0.84) and in the TCI group whenever the length of the procedure was over 60′ (r = 0.94)

	Baseline	Block	Incision	End
TCISBP	148 ± 25	128 ± 23	119 ± 20	128 ± 14
TCIDBP	85 ± 11	77 ± 12	66 ± 15	68 ± 13
TCIHR	83 ± 20	77 ± 12	70 ± 13	73 ± 20
NSSBP	141 ± 31	129 ± 20	130 ± 16	127 ± 10
NSDBP	82 ± 13	71 ± 9	74 ± 28	68 ± 13
NSHR	79 ± 21	105 ± 15	96 ± 12**	97 ± 10*

**p < 0 01, *p < 0 05

Conclusions: A TCI of propofol provides easy control of sedation and does not alter blood pressure in SA block

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A.412 Sedation during regional anaesthesia for orthopaedic surgery: propofol *vs* remifentanil

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The use of sedation during R. A. can provide enhanced patient comfort while optimazing intraoperative conditions (1). The aim of this study is to compare the sedative effects of Propofol and Remifentanil (2) in 40 patients undergoing elective orthopaedic surgery.

Methods: Patients, ASA I–II, 37 years mean age, were randomized in 2 groups of 20 each. ECG, B.P., H.R., R.R. and SpO_2 were monitored throughout the procedure. The R A techniques, biblock and brachial plexus block, were comparable in both groups. After Intravenous Atropine, group A received Propofol (1.5 $mg{\cdot}Kg^{-1}{\cdot}h^{-1}$), while group B Remifentanil (0.1–0.2 $mcg{\cdot}Kg^{-1}{\cdot}min^{-1}$), with a continuous infusion pump, to maintain sedation all over the procedure, with a constant rate of Propofol infusion, while Remifentanil's rate was subsequently titrated due to the respiratory and haemodinamic effects (bradycardia and hypotension), for the better patient comfort. Sedation's level was rated before the block, at 15 m′ of intervals and at the end of the procedures, on a five point sedation scale (from 1 = fully awake, to 5 = unrousable to mild physical stimulation) (3).

Results: Sedation vanished in 1–2 m′ after the infusion stopped Nobody among the 2 groups had respiratory or haemodinamic complications Similar sedative effects were demonstrated, even if Remifentanil was a better analgesic adjuvant when the blocks were uncomplete; sedation's level was conditioned by patients' age and O.R.'s noisy: no one has been fully awake or unrousable to mild physical stimulation; 15 pts (75%) in group A and 17 (82%) in group B were lightly sedated and rousable to spoken commands; only 5 (25%) in group A and 3 (18%) in the other one were rousable to mild physical stimulation (earlobe tug). All the pts left the O.R. completely awake and no PONV occurred; fluids and analgesics, as required, could be taken orally almost immediately.

Conclusions: Propofol and Remifentanil give both a good sedation during R.A. Remifentanil offers us an analgesic effect too, but to achieve the desired results it's necessary a vigilant continuous monitoring and a careful dose titration, which is sometimes difficult, especially for young patients.

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A.413 Sedation during spinal anaesthesia: comparison of haemodynamic, anxiolytic and amnesic effects of propofol and midazolam

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Introduction: Supplementary sedation for spinal anaesthesia can enhance patient comfort and increase acceptance of this technique. The aim of this study was to compare the haemodynamic, anxiolytic and amnestic effects when either midazolam or propofol was given by subanaesthetic infusion to provide sedation as an adjunct to spinal anaesthesia.

Method: After Informed consent and approval by the Ethics Committee 45 patients ASA I–II, undergoing surgical procedures with spinal anaesthesia were randomly assigned to one of three groups. Control (Group C) received no sedative-hypnotic agent; Propofol (Group P) received a loading dose of 1 mg/kg followed by an infusion of 4 mg/kg/hr; Midazolam (Group M) received a loading and infusion dose of 0 1 mg/kg. The infusion rates were adjusted to maintain an appropriate level of sedation (level 3–4) on a five-point sedation scale The sedative infusion was stopped 10 minutes before the anticipated end of the procedure. The sedation score, the systolic, diastolic, mean arterial pressures (SAP, DAP, MAP), heart rate (HR), respiratory rate (RR) and oxygen saturation (SaO_2) values were recorded before spinal block, after spinal block and at 5-minute intervals throughout the surgical procedure Visual analogue scales (VAS) were used to assess pre- and postoperative anxiety. In the Recovery Unit, the times taken from the end of the infusion for patients to open their eyes on command and to given correct responses to the questions about name-place-time were noted. To assess intraoperative recall, a simple picture was shown to the patients by rousing them during the operation.

The results were analyzed statistically using Kruskal-Wallis, ANOVA, Mann Whitney U and Chi-square tests.

Results: The three groups were similar demographically. There were statistically significant decreases in SAP, DAP and MAP values in Group P where the decreases were statistically insignificant in Group M There were statistically significant increases in respiratory rates in Group P and Group M beginning from the 5th and 15th minutes of infusion respectively Postoperative anxiety scores of Group P and Group M were statistically lower than Group C ($p < 0.05$). Amnesia was significantly greater with midazolam (80%).

Conclusion: Both propofol and midazolam by intravenous infusion provide satisfactory sedation as an adjunct to spinal anaesthesia. Midazolam, for its amnestic and stable haemodynamic effects and propofol, for its rapid recovery are evaluated as preferred agents for supplementary sedation

A.414 Haemodynamic effects of general anaesthesia and intravesical bupivacaine for endoscopic bladder surgery

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The majority of endoscopic procedures are performed under spinal or general anesthesia Lidocaine gel can be used locally for topical urethral anesthesia However, this is not appropriate for endoscopic bladder surgery (1). In this study we compared the hemodynamic effects of intravesical bupivacaine and general anesthesia.

Material & Methods: After Institutional approval, fifty ASA II, III patients undergoing endoscopic bladder surgery were recruited (HR) (beats/min) was recorded and (MAP) (mmHg) monitoring was performed. Patients were randomly allocated into two groups. Group I: Anesthesia was obtained by giving 10 cc of 2% lidocaine hydrochloride gel in the urethra and instillation of 60 cc of 0.5% bupivacaine hydrochloride via a Foley catheter. Group II: Induction of anesthesia is obtained with 2–3 mg/kg propofol, 0.5 mg alfentanyl IV and maintained with N_2O %50 in 50% O_2 and 2 mg/kg propofol infusion MAP and HR measurements were recorded every 5 minutes. The data were statistically analyzed with paired-t test.

Results: Demographic data and duration of operation were similar in both groups (Table 1). MAP and HR were not different compared to baseline in group I, whereas they were significantly reduced in 5 and 10 minutes in group II ($p < 0.05$). Check cystoscopies together with selected area biopsies were performed without any pain to the patient in both groups.

Hemodynamic parameters

MAP (mmHg)	Baseline	5 min	10 min
Group I	111 8 ± 3 8	108 ± 3 2	109 2 ± 3 2
Group II	107 8 ± 2 5	76.6 ± 1 2*	78 2 ± 1 5*

HR (beats/min)	Baseline	5 min	10 min
Group I	74.1 ± 2 8	73 6 ± 3 2	73 1 ± 0.8
Group II	76 0 ± 1 4	63 5 ± 0 6*	63 1 ± 0 8*

Conclusions: Our data show that lidocaine gel for urethral anesthesia and 60 cc of 0 5% bupivacaine hydrochloride instillation into the bladder provide adequate anesthesia and analgesia for endoscopic bladder surgery Intravesical bupivacaine anesthesia causes less hemodynamic disturbances compared to general anesthesia These observations may greater impact in elderly and high risk patients

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A.415 Urapidil for the treatment of postepidural shivering. A preliminary study

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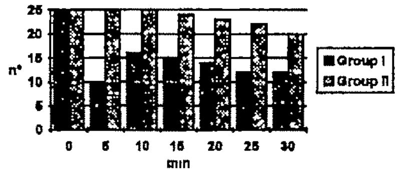
Background & Goal of Study: there is evidence that both drugs acting on α-adrenergic and on 5-hydroxytryptamine (5-HT) receptors reduce post-anaesthetic shivering[1]. Urapidil (U), an antihypertensive drug acting on α^1-adrenergic and 5-HT_{1A} receptors, suppressed cold induced shivering in volunteers[2]. This study investigated the efficacy of U in suppressing post-epidural shivering.

Materials and Methods: 50 healthy patients, aged 18–45, who developed shivering after epidural anaesthesia, were randomly allocated into two groups of 25 Group I received i.v U 25 mg, group II received a saline bolus Shivering was assessed just before treatment (0 min = baseline) according to a three-point scale: 0 = no shivering, 1 = moderate, 2 = severe Shivering grade, systolic arterial pressure and heart rate were assessed every 5 min for a period of 30 min starting from baseline Hypotension was defined as a 20% reduction in SAP in relation to baseline value. Data were analysed using t-test, Mann-Whitney U-test and chi-squared test as required.



Results: U was more effective than placebo in suppressing shivering (P < 0 001 at 5 min; P < 0.005 at 10 min, P < 0 01 at 15, 20 and 25 min, P < 0 05 at 30 min) (see fig 1). The severity of shivering was significantly lower in group I at 5 and 10 min (p < 0 05). In group I six patients recommenced shivering after they had stopped Five patients in group I and none in II had hypotension (P = 0.059.

Conclusions: U 25 mg was effective in treating post-epidural shivering However 30% of the patients who had stopped after U administration, recommenced shivering within 5 min A non significant trend toward a greater incidence of hypotension was recorded in group I Larger studies are needed to evaluate the benefits of this method.

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A.416 Incidence of hypotension during thoracic epidural anaesthesia combined with general anaesthesia: fentanyl plus etomidate *vs* ketamine plus midazolam

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Background and Goal of Study: Thoracic epidural anesthesia (TEA) combined with general anesthesia (GA) can produce hypotension, the incidence of which may be related, among other factors, to the type of GA Ketamine and etomidate preserve the efferent sympathetic nerve activity and autonomic reflex function; in addition, ketamine produces sympathetic stimulation We proposed to determine whether induction of GA with a combination of ketamine plus midazolam was associated with lower incidences of hypotension and bradycardia than induction with fentanyl plus etomidate

Material and Methods: A series of 82 adult patients, ASA class II–III, who were to undergo abdominal surgery was studied All of the patients underwent placement of a thoracic epidural catheter (D_6–D_8) and received 6–12 ml of 2% lidocaine, continued at a rate of 4–9 ml/h. The patients were prospectively randomized to Group I (n = 41), in whom anesthesia was inducted by ketamine (2 mg/kg) plus midazolam (0 1 mg/kg) plus vecuronium (0.15 mg/kg), and Group II (n = 41), who received etomidate (0 2–0 3 mg/kg) plus fentanyl (5 μg/kg) plus vecuronium (0 15 mg/kg) Maintenance was achieved with 50% O_2 plus 50% air plus 0.5–1% isoflurane in both groups. Heart rate (HR) and systolic blood pressure (SBP) were measured noninvasively once every minute until intubation and every 3 minutes thereafter until skin incision We defined 3 levels of hypotension – SBP < 100 mmHg, SBP < 90 mmHg and SBP < 80 mmHg – as well as bradycardia HR: < 50 bpm. The data were analyzed using the χ^2 test and comparison of proportions and the χ^2 test with Yates' correction was used when the expected frequency was under 5% A p value of less than 0 05 was considered to indicate statistical significance

Results and Discussion: The observation period had a minimum duration of 40 minutes.

	SBP < 100 mmHg	SBP < 90 mmHg	SBP < 80 mmHg	HR < 50 mmHg
Group I %	26.8	17	9 7	7 3
Group II %	70 7	29 2	4 8	29 3
p value	<0 05	>0 05	>0 05	<0 05

Conclusions: In TEA combined with GA, induction with ketamine plus midazolam is associated with a lower incidence of mild hypotension and bradycardia than induction with etomidate plus fentanyl

A.417 Pharmacokinetics of epidurally administrated liposomal bupivacaine in humans

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Introduction: Liposomes associated with aminoamides, prolong sensory anesthesia and reduce peak plasma levels of aminoamide when injected epidurally in animals (1–4). To determine the validity of this statement in humans, we evaluated the effect of liposome encapsulation of bupivacaine on the course and extent of systemic arterial concentrations of bupivacaine after epidural administration of liposome encapsulated bupivacaine

Methods: Liposomes associated bupivacaine were prepared in sterile and aseptic conditions as described before (5). Following approval by the University Committee on Human Research, 14 patients (ASA I–III) scheduled for abdominal surgery, received an epidural catheter inserted to at L2 level and a 3 ml test dose of xylocaine 2% with 1/200 000 adrenaline Then, 10 ml of either bupivacaine 0 5% (group BUPI) (n = 7) or liposome associated bupivacaine 0 5% (group LIPO) (n = 7) were injected epidurally After a 30 min observation period, a general anesthesia was started and surgery allowed to proceed Meanwhile, plasma arterial blood samples were taken before injection at 5, 10, 15, 30, 45 min and at 1, 2, 3, 4, 6, 12 and 24 h to determine plasma bupivacaine levels Plasma bupivacaine levels were determined with HPLC (detection limits of 10 ng/ml) All data are expressed as mean value ± SD. Differences between groups were identified with ANOVA and MWU-test. P < 0 05 values were considered statistically significant

Results: Both groups demonstrated similar demography The profile of the bupivacaine concentrations revealed a lower peak concentration in group LIPO (mean 351 ± 135 ng/ml; range 166–562 ng/ml) vs group BUPI (mean 554 ± 126 ng/ml; range 450–757) $T_{max-Lipo}$ (28 ± 12 min, range 15–45 min) was delayed vs $T_{max-Bupi}$ (10 ± 3 min, range 5–15 min) Plasma levels of bupivacaine in group LIPO revealed an increased terminal decline half-life (451 ± 210 min vs 327 ± 145 min).

Conclusion: This human study demonstrated that after epidural administration of liposomes associated bupivacaine peak plasma levels were reduced and T_{max} delayed The current formulation is associated with a prolonged release of bupivacaine

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PHARMACOLOGY

A.418 Intubating characteristics and duration of clinically effective block after two different doses of cisatracurium

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Background and Goal of Study: Cisatracurium is one of ten stereoisomers of atracurium, being more potent with a mean ED95 in adults during opioid anaesthesia of 0.05 mg/kg (1) This study simulated routine clinical practice and compared the time to satisfactory intubating conditions and the duration of clinical block of two different doses of cisatracurium

Materials and Methods: 95 healthy adult patients were entered into this randomised, open-label study. Following premedication, anaesthesia was induced with propofol and fentanyl; patients were allocated to receive cisatracurium either 0.10 mg/kg or 0.15 mg/kg, and anaesthesia maintained with N_2O in oxygen supplemented with isoflurane.

Intubation was attempted 2 minutes after administration of cisatracurium and graded according to standard criteria. Neuromuscular transmission was monitored by tactile evaluation of the adductor pollicis response to train-of-four (TOF) stimulation. If required, further doses of 0.03 mg/kg cisatracurium were given on the reappearance of the third response to TOF stimulation. Recovery from block was spontaneous or pharmacologically augmented at the investigators' discretion, and was assessed using a combination of clinical criteria and tactile response to TOF

Results and Discussion: At the first intubation attempt (median time 2 minutes in each group) 42 (91%) of patients in the 0.10 mg/kg group and 47 (98%) of patients in the 0.15 mg/kg group were satisfactorily intubated. There was no significant difference between treatments when assessing the time to intubation; however, the first intubation grades suggested that patients receiving 0.15 mg/kg had better conditions than patients receiving the 0.10 mg/kg dose ($p = 0.002$). Clinical duration of block, as measured by the return of the third response to TOF stimulation, was significantly shorter in the 0.10 mg/kg group than in the 0.15 mg/kg group (median time 37 minutes vs 47 minutes respectively, $p < 0.001$). There were no reports of inadequate reversal, either spontaneous or augmented, and no serious adverse events were described.

Conclusions: The intubating conditions and duration of clinical block support a dose of 0.15 mg/kg, which provides satisfactory intubating conditions at two minutes and approximately 45 minutes of clinical block, which can either be allowed to recover spontaneously or may be readily reversed pharmacologically, once signs of spontaneous recovery are present.

Study funded by a research grant from Glaxo Wellcome

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A.419 Duration and recovery profile of cisatracurium after suxamethonium during propofol and isoflurane anaesthesia

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Background: The duration to 25% recovery following an intubating dose of cisatracurium (CA) 0.2 mg/kg is about 1 hr with nitrous-narcotic technique (1) and even longer with inhalational agent. There is paucity of data on the duration of action of CA when administered after succinylcholine (S) This study determines the duration of action and recovery profile of small doses of CA following S during propofol and isoflurane anesthetics.

Methods: Forty ASA 1 & 2 adult patients having elective surgery with general anesthesia lasting longer than 90 min were enrolled after IRB approval and written informed consent. All patients received midazolam 1–3 mg as premedication. General anesthesia was induced with propofol 1–2 mg/kg. Datex 221 NMT was used to record the response of the adductor pollicis after supramaximal stimulation of the ulnar nerve. A baseline EMG was obtained after induction An intubating dose of S 1.5 mg/kg was administered The tracheal was intubated when the first twitch of the evoked train-of-four (TOF) reached ≤10% of control Spontaneous recovery from neuromuscular blockade was allowed to occur until the first twitch (T1) returned to 25% of control. Patients were then randomized to receive CA as follows. Group 1: 0.025 mg/kg (0.5XED95); Group 2: 0.05 mg/kg (ED95); Group 3: 0.05 mg/kg (ED95) and Group 4: 0.1 mg/kg (2XED95). Patients in Groups 1 and 2 were maintained with isoflurane 1–2%, 66% N_2O in O_2 while patients in Groups 3 and 4 were maintained with propofol 80–160 μg/kg/min, 66% N_2O in O_2. Temperature was maintained above 35°C and end-tidal CO_2 was maintained between 30–40 mmHg The TOF evoked EMG was recorded at 10 s intervals. The time for the evoked EMG to spontaneously return to 25, 50 and 75% of the original baseline was noted. Descriptive statistics and Kruskal-Wallice test were performed. A $p < 0.05$ was considered statistically significant.

Results: There were 10 patients in each group. Patient demographics were similar between groups. In group 1 (0.025 mg/kg), only 3 out of 10 patients had $T1 < 25\%$. Table 1 shows time to lowest T1 and the recovery profile.

Time to	Isoflurane Groups		Propofol Groups	
	1/2XED95	ED 95	ED 95	2XED95
Max block*	6.1 ± 2.1	5.3 ± 3.15	4.6 ± 2.2	3.4 ± 2.2
T1 = 25%*	N/A	24.5 ± 10	21.3 ± 9	40.2 ± 7
T1 = 50%*	N/A	33.8 ± 14	27 ± 9	47.5 ± 8
T1 = 75%*	11 ± 8.3	42.2 ± 18	32.8 ± 4	59.7 ± 19
T1 25–75%	N/A	19.4 ± 4.2	16 ± 8.7	19.6 ± 8.5

All times are in min. Mean ± SD * = $p < 0.01$

Conclusions: CA 0.05 mg/kg (ED95) provides 20–25 min. of neuromuscular blockade after intubating dose of S. CA 0.025 mg/kg (1/2XED95) is an inadequate dose in this setting. Doubling the dose of CA resulted in twice the duration of action under propofol anesthetic. The recovery profile of CA is predictable following S during isoflurane and propofol anesthetic

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A.420 Effects of atracurium in thymectomy for myasthenia gravis

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Background and Goal of Study: Myasthenia gravis is an autoimmune neuromuscular disorder that shows increased sensitivity to nondepolarizing muscle relaxants. Atracurium is eliminated by Hofmann elimination and ester hydrolysis. We studied the onset and duration of atracurium in patients with myasthenia gravis.

Materials and Methods: Ten patients undergoing thymectomy for myasthenia gravis and ten patients of ASA class I–II without liver, kidney and neuromuscular disease for orthopedic surgical procedures were assigned to two groups: control and myasthenia gravis.

Anesthesia was induced with thiopental and maintained with inhalation of N_2O-O_2 (1:1) and isoflurane (0.5–1.5 vol%). Atracurium (0.5 mg/kg) was given as a muscle relaxants and then intubation was performed after twitch response was depressed more than 80%. Neuromuscular relaxation was assessed by TOF (T1) at the adductor pollicis with supramaximal stimulation of ulnar nerve at 2 Hz every 12 seconds. The onset and duration of 5, 25, 50, 75% recovery time of T1 and recovery index were recorded.

Results & Discussion: Onset of block was shortened and recovery time of 5, 25, 50, 75% and recovery index were prolonged in patients with myasthenia gravis.

Onset, Duration and Recovery Index of Atracurium

	Control	Masthenia Gravis
Onset time (min.)	3.4 ± 1.4	1.3 ± 0.3*
Recovery time (min.)		
5%	33.2 ± 8.0	65.0 ± 31.6*
25%	42.1 ± 9.0	72.2 ± 38.3*
50%	49.9 ± 10.8	94.2 ± 45.8*
75%	58.6 ± 12.9	112.8 ± 59.9*
Recovery index	16.4 ± 5.6	35.6 ± 33.2*

Mean ± S.D., *$p < 0.05$ Compared with control group

Conclusions: Atracurium in the patients with myasthenia gravis induced rapid onset and prolonged recovery time of 5, 25, 50, 75% and recovery index

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A.421 Antagonism of neuromuscular block after magnesium sulphate pretreatment

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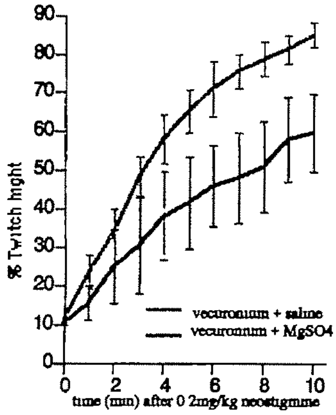
Background: Magnesium sulphate ($MgSO_4$) may be given in the perioperative period for several reasons (1). $MgSO_4$ prolongs clinical duration and delays recovery of vecuronium neuromuscular (NM) block (2). Thus, residual paralysis occurs in this patient population (3) No prospective data about antagonisation of vecuronium NM block when used together with $MgSO_4$ are available. This study aims to investigate the impact of neostigmine (N) on vecuronium NM block with and without $MgSO_4$ pretreatment.

Patients & Methods: After ethics committee approval and informed consent, 20 patients ASA I–II were included and randomly assigned to one of two groups receiving either 60 mg/kg $MgSO_4$ or saline (n = 10 in each). In both groups anaesthesia was induced by thiopentone (5 mg/kg), fentanyl (2 μg/kg) & vecuronium (0.1 mg/kg), maintained by isoflurane (1%) and N_2O/O_2. No further muscle relaxant were given. NM blockade was assessed by electromyography (Relaxograph®). Once the NM block recovered to a twitch height (TH) of 10%, patients in both groups received N (0.02 mg/kg) and recovery of NM block assessed (TH) once a minute over 10 min. Between group comparison of the respective TH values was made using a Mann-Whitney *U* test, significance was set at $P < 0.05$.

Results: The response of TH after N was less pronounced in the $MgSO_4$ group When compared to the control group, this difference was significant over the whole study period (10 min).



Conclusion: $MgSO_4$ led to an attenuation of neostigmine-induced recovery of vecuronium-NM block (Fig 1). This may be the result of prolonged recovery of NM block after $MgSO_4$ (2) or a $MgSO_4$ induced decrease of the neostigmine response.

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A.422 Spontaneous or neostigmine-induced recovery after three maintenance doses of Org 9487

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Background: Initial studies with Org 9487, a new short-acting aminosteroidal muscle relaxant, have suggested that an intubating dose of 1 5 mg kg^{-1} may be antagonised rapidly with neostigmine within 2 min of administering Org 9487 [1]. We have undertaken a study comparing recovery after 3 maintenance doses or a 30 min infusion of Org 9487, or after 2 maintenance doses of rocuronium with and without neostigmine after an initial bolus of Org 9487. The results of the 3 maintenance doses of Org 9487 are presented here.

Methods: Thirty patients were anaesthetised with propofol 1.5–2 5 mg kg^{-1} and alfentanil 30 $\mu g\ kg^{-1}$ followed by propofol and alfentanil infusions and 60% nitrous oxide in oxygen. The ulnar nerve was stimulated with supramaximal train-of-four (TOF) stimuli and the force of contraction of the adductor pollicis recorded All patients were to receive an intubating dose of Org 9487 1.5 mg kg^{-1} and 3 maintenance doses of 0.5 mg kg^{-1} each time the T_1 (the first response in the TOF) recovered to 25% Patients were allocated at random to receive no reversal (Group I) or neostigmine 0.05 mg kg^{-1} (Group II) at T_1 to 25% after the last dose The times of recovery of TOF ratio to 0 8 and the recovery indices (RI, T_1 25–75%) were recorded

Results and Discussion: The mean (SD) Dur_{25} (time to recovery of T_1 to 25%) of the initial 1 5 mg kg^{-1} dose was 16.8 (4.0) min (n = 26). Dur_{25} of the 3 successive maintenance doses increased significantly from 12.2 (3.4) min (n = 26), to 14 0 (4 0) (n = 26), and 15.9 (5.9) min (n = 25) (P < 0 01, one sided Page's test) Administration of neostigmine on recovery of T_1 to 25% after the last maintenance dose resulted in significantly shorter times to TOF ratio of 0.8 and the RI (Table 1; P < 0 01; t test with Welch's correction)

Recovery times (min) (mean (SD))

	T_1 25%-TOF 0 8	RI
Group I (n = 11)	72 4 (16 5)	24 5 (13 6)
Group II (n = 14)	9.9 (4 5)	3 6 (1 8)

Conclusion: The results from the present study suggest that repeat doses of Org 9487 are associated with an increase in duration of action and slow spontaneous recovery compared to a single dose [1] Administration of neostigmine at T_1 of 25% results in a rapid reversal.

Supported by Organon Teknika

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A.423 Action duration of atracurium and vecuronium in renal transplantation

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Background and Goal of Study: Atracurium is eliminated by Hofmann elimination and ester hydrolysis, with minimal renal and hepatic excretion Vecuronium is less dependent on the renal function than other steroid type neuromuscular blockers. But the action duration of vecuronium is prolonged in renal failure. The purpose of this study is to compare the differences of the effects of atracurium and vecuronium in patients with and without renal function

Material and Methods: Forty patients with normal renal function and 40 patients with chronic renal failure were assigned to one of four groups. atracurium-normal (n = 20, AC), atracurium-renal failure (n = 20, AK), vecuronium-normal (n = 20, VC), vecuronium-renal failure (n = 20, VK) Anesthesia was induced with thiopental and maintained with inhalation of N_2O (50%) and isoflurane (0 5–1 5vol%) Atracurium (0 5 mg/kg) or vecuronium (0 1 mg/kg) was given as a muscle relaxant and then endotracheal intubation was performed after twitch response was depressed more than 80%. Neuromuscular blockade was assessed by TOF at the adductor pollicis with supramaximal stimulation of ulnar nerve The onset time, duration of 5, 25, 50, 75% recovery time and recovery index were recorded.

Results & Discussion: Onset of block was not different among four groups. Recovery time of 5 25 50, 75% and recovery index were significantly longer in the both renal failure groups. Action duration in renal failure were not different between atracurium and vecuronium groups

Comparison of the onset time, recovery time and recovery index of the atracurium and vecuronium

	Atracurium		Vecuronium	
	AC	AK	VC	VK
Onset time (min)	2 9 (1 2)	2 9 (1.3)	2 9 (0 5)	2 5 (0 6)
Recovery time (min)				
5%	34 0 (10 8)	43 8 (20 4)*	26 2 (3 7)	54 9 (22 4)#
25%	42 6 (12 9)	60 7 (23 6)*	33 9 (5 4)	77 1 (33 5)#
50%	50 0 (15 6)	72 5 (25 8)*	38 9 (9)	89 6 (39 5)#
75%	55 7 (20 4)	85 0 (28 9)*	44 8 (9 6)	100 6 (39 0)#
Recovery Index	15 1 (8 4)	24 8 (13 4)*	10 9 (5 5)	25 6 (9 8)#

Values are Mean (SD) *, p < 0 05 Compared with atracurium control (AC) group #, p < 0 01 Compared with vecuronium control (VC) group

Conclusions: It is concluded that renal function is influenced action duration of atracurium and vecuronium. In renal failure there were no differences in action duration between the both relaxants

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A.424 Pharmacokinetic interaction between propofol and alfentanil in healthy male volunteers

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Background & Goal of the Study: Although the pharmacodynamic interaction between propofol (PROP) and alfentanil (ALF) has been described in detail, very little is known on whether PROP affects the pharmacokinetics of ALF We studied the effect of a semi-steady-state concentration of PROP on the pharmacokinetics of ALF.

Materials and Methods: With ethics committee approval and informed consent the pharmacokinetics of ALF were studied during 2 sessions in 8 healthy male volunteers in the presence and absence of PROP in a randomized, cross-over manner. While breathing 30% O_2 in air, ALF 12.5 μg/kg, iv, was given in 2 min, followed by 25 μg/kg/h for 58 min (session A) During session B, a target-controlled infusion of PROP, (target-concentration 1.5 μg/ml) was started 15 min before the start and maintained until 6 h after termination of the ALF infusion The interval between sessions was 3 weeks. The ECG, BP, RR, $ET\text{-}CO_2$, noninvasive CO and SaO_2 were monitored. The $ET\text{-}CO_2$ was maintained at 4 0–4.5 kPa Venous blood samples for plasma ALF and blood PROP determination were taken frequently during and until 6 h after termination

The pharmacokinetic parameters of ALF and the haemodynamic data in the presence and absence of propofol

	Session A	Session B	Difference (%)	P-value
V_1 (ml/kg)	191 ± 95	76 ± 23	−60	0 01*
V_{ss} (ml/kg)	393 ± 81	347 ± 42	−9	0 18
CL (mg/kg/min)	4 8 ± 1 5	3 9 ± 1 0	−19	0 07
CL_d (mg/kg/min)	9 4 ± 5 9	22 3 ± 24 9	137	0 19
$t_{1/2}$ alpha (min)	7 9 ± 4 8	2 2 ± 0 8	−72	0 01*
$t_{1/2}$ beta (min)	70 ± 9	74 ± 14	6	0 3
lag time (sec)	109 ± 14	38 ± 40	−65	0 0002*
CI (l/m^2)	3 28 ± 0 37	3 13 ± 0 38	−5	0 28
MAP (mmHg)	81 ± 6	69 ± 5	−15	<0 001*
SVR ($dynes/sec/m^{-5}$)	1006 ± 107	908 ± 109	−10	0 05*

of the ALF infusion The pharmacokinetics of ALF were determined using WINNONLIN and compared between sessions A and B with the paired t-test

Results and Discussion (see Table)· The mean (± SD) age and weight of the volunteers were 24 ± 3 yr and 74 ± 6 kg. The data were best fitted with a 2-compartment pharmacokinetic model. A lag time was included in the model because of venous sampling

Conclusion: Propofol affects the pharmacokinetics of alfentanil, in particular the initial distribution This may be explained by the haemodynamic changes induced by PROP in session B

A.425 Cerebrospinal fluid concentration of propofol during anaesthesia in man

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Background: The concentration of propofol in and surrounding the brain during propofol anaesthesia is unknown. Knowledge of this concentration is crucial for delineating the mode and specificity of action of propofol at molecular and cellular levels Previous *in vitro* studies investigating the intracellular effects of propofol and its action on the $GABA_A$ receptor have used propofol concentrations of 3 µg/ml to mimic clinical anaesthesia (1)

Materials and Methods: We simultaneously measured the concentration of propofol in cerebrospinal fluid (CSF) from an indwelling intraventricular catheter and the concentration in arterial blood in 5 neurosurgical patients before, during induction (at 2.5 and 5 minutes) and during a maintenance propofol infusion (at 15 and 30 minutes) After an induction dose of 2 mg/kg bw given over 2 minutes, anaesthesia was maintained with an infusion of 8 $mg.kg^{-1}\ h^{-1}$ for 15 minutes and then reduced to 6 $mg.kg^{-1}\ h^{-1}$. The propofol concentration in CSF and plasma was determined by high-performance liquid chromatography with fluorescence detection (2)

Results: The concentration of propofol in blood showed a predictable course and reached a pseudo-steady-state concentration of 10–20 µmol/L (1.5–3.0 µg/ml) after 5 minutes. The CSF concentration of propofol increased 2 5 minutes after induction and a plateau concentration of 0.2–0.3 µmol/L (30–50 ng/ml) was observed 15 minutes after induction.

Conclusion: The CSF concentration of propofol we demonstrated is less than 10% of the plasma concentration and is consistent with the high protein binding of the drug in plasma (3). If the propofol concentration measured in the CSF is equivalent to the free concentration in brain interstitium it suggests that the much higher concentrations used to investigate the actions of propofol on neurons *in vitro* may not be relevant to the clinical setting.

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A.426 Midazolam concentrations in serum and cerebrospinal fluid after epidural administration in dogs

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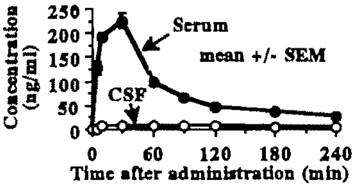
Background and Goal of Study: Epidural administration of midazolam has analgesic effects on postoperative somatic pain[1]. However, high dose midazolam induces sedation, amnesia and some muscle weakness. These effects by central nervous system (CNS) might be due to midazolam come through systemic circulation or cerebrospinal fluid (CSF). The purpose of this study was to elucidate by which way midazolam goes up to CNS in measuring midazolam concentrations in serum and CSF after epidural administration.

Materials and Methods: After the approval by our institutional review board, five mongrel dogs (8 to 12 kg) were anesthetized with intramuscular ketamine 20 mg/kg, then intravenous thiopental 5 mg/kg. Anesthesia was maintained with isoflurane 2% in oxygen (40%)–air mixture after tracheal intubation with vecuronium 0.5 mg/kg. Femoral artery was cannulated for blood pressure and pulse rate (heart rate) measurements and blood collection. Dorsal L3-4 region was clipped, 3 cm midline skin incision was made, muscles were gently dissected from the vertebrae, and 20 G epidural catheter was inserted using a loss of resistance technique like clinical procedure. Atlanto-occipital region was also clipped, 3 cm skin was incised, muscles were dissected, and 19 G catheter was inserted into intrathecal space to collect CSF Midazolam 1 mg/kg was injected epidurally Blood and CSF were drawn before, 5, 10, 30, 60, 90, 120, 180 and 240 minutes for the measurement of midazolam concentration. The measurement was done by gas chromatography (Teijin Bio Lab. Tokyo, Japan). Statistical analysis was performed with repeated measures analysis of variance followed by Fisher's protected least significant difference. $P < 0.05$ was considered to be significant

Results and Discussion: Blood pressure decreased and heart rate increased significantly 5 and 10 minutes and then went back to the control levels Serum concentrations of midazolam were significantly higher than CSF concentrations (Figure) Central effects of epidural midazolam was suggested to come through systemic circulation not by going up through CSF



Conclusions: Serum concentration of midazolam was significantly higher than CSF concentration after epidural administration It suggests the central effects of epidural midazolam come through systemic circulation

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A.427 Serum concentrations of the enantiomers of tramadol during patient-controlled analgesia

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Background & Goal of Study: Tramadol, a centrally acting analgesic, is used as a racemate containing 50% of a (+)- and 50% of a (−)-enantiomer. 98 patients recovering from major gynaecological surgery were treated in a randomised, double-blind study with (+)- tramadol, (−)-tramadol or the racemate [1]. Following an i.v. bolus up to a maximum of 200 mg, patient-controlled analgesia with demand doses of 20 mg was made available for 24 hours. The clinical results showed that (+)-T and racemate were more potent analgesics than (−)-T, whereas the incidence of adverse events was higher in (+)-T patients than in racemate patients This abstract presents the pharmacokinetic results in 92 patients.

Materials & Methods: Prior to each demand, the serum concentrations of the enantiomers of tramadol and its metabolite M1 were measured The concentrations of (+)-T and (−)-T were determined by a modified gas chromatographic-mass spectrometric method on a column coated with CP-Cyclodextrin-β-2,3,6-m-19; the (+)-M1 and (−)-M1 concentrations were determined after derivatisation with diazoethane by gas chromatography on the same above mentioned column and with a nitrogen-selective (NDP) detector. Analysis of variance including Scheffe's test for pair-wise comparison was used to compare the concentrations between the 3 treatment groups (SPSS, $p < 0.05$)

Results & Discussion: The mean concentrations of (−)-T and (−)-M1 in the (−)-T group were higher than those of the sum of (+)- and (−)-T and of (+)-M1 and (−)-M1 in the racemate group, which in turn were greater than those of (+)-T and (+)-M1 in the (+)-T group ($p < 0\ 05$)

Therapeutic serum concentrations of tramadol and the metabolite M1 in the 3 treatment groups

Treatment group	Analysed substance	Patients n	ng/ml mean ± SD
(+)-T	(+)-T	32	470 ± 323
racemate	T_{sum}	28	590 ± 410
(−)-T	(−)-T	32	771 ± 451[a]
(+)-T	(+)-M1	27	57 ± 18
racemate	$M1_{sum}$	22	84 ± 34[b]
(−)-T	(−)-M1	32	96 ± 41[b]

T_{sum} = (+)-T + (−)-T, $M1_{sum}$ (+)-M1 + (−)-M1 [a] difference to (+)-T statistically significant; [b] difference to (+)-M1 statistically significant

Conclusion: The presented pharmacokinetic results are in agreement with the clinical findings that the racemate is superior to either enantiomer alone.

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A.428 Antinociceptive/anti-oedema effects of free and liposomal morphine in a rat model of carrageenan-induced arthritis

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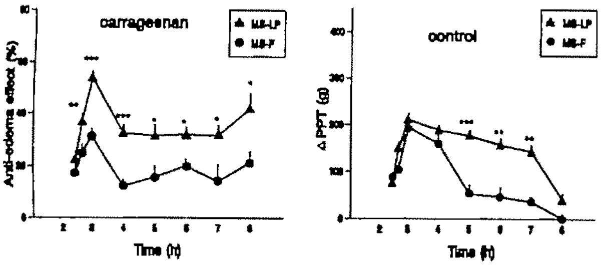
Background: Liposomes are used to slow active-drug delivery and decrease toxicity. In animals, liposomal morphine (MS-LP) has a more sustained analgesic effect and decreased toxicity. Acute inflammation sensitizes opiate receptors and enhances the peripheral effects of opiates (1). Our hypotheses was that during inflammation, MS-LP would maintain the enhanced antinociceptive effects manifested by free morphine (MS-F), while showing a longer duration of action.

Methods: we evaluated the antinociceptive and anti-edema effects of s c MS-F and MS-LP, in a rat model of carrageenan induced inflammation. Antinociception was evaluated by paw pressure threshold (PPT) and edema, by measuring the volume of the paw

Results: the antinociceptive effects of MS-F were increased 2 6 times during inflammation, while that of MS-LP was unaltered MS-LP was twice as potent as MS-F in non injected animals. For the anti-edema effects, MS-LP produced a more prominent ($P < 0\ 01$) and prolonged effect ($P < 0\ 05$) than MS-F. In carrageenan treated animals, MS-F had a higher peak for PPT but duration was prolonged by encapsulation ($P < 0\ 01$) In non inflamed (control) animals, MS-LP had a longer duration and the area under curve increased 40%. The effects of MS-F were completely reversed by naloxone, while those of MS-LP were partially antagonized



Discussion: inflammation enhances the antinociceptive effects of free but not liposomal morphine, while encapsulation increases the duration of action. The anti-edema effects are more pronounced and sustained after encapsulation. We concluded that MS-LP manifests a better anti-edema effect with a more prolonged antinociceptive action

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A.429 Experimental *In vitro* release studies of morphine liposomal association

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Background: Most trials concerning the entrapment of morphine used high concentrations and amounts of the opioid (1) or large multivesicular liposomes (2). This leads to the administration of supraclinical doses entrapped in the liposomal aqueous phase. We studied the association and release of this amphophilic compound (pKa 7.9) inserted into the phospholipid bilayers at concentrations relevant for clinical practice.

Materials and Methods: Liposomal morphine (lipo-MP) formulations were prepared from lipid films of egg phosphatidylcholine (EPC)/cholesterol/α-tocopherol (molar ratio 4 3 0 07) and quantities of apolar morphine (MP) 2, 5 and 10 mg so that the EPC/MP mole ratio range was 26 1, 10.1 and 5.1 ($n = 3$) The morphine-liposome association efficiency increased from 85% to 95% and around 100% respectively The multilamellar vesicles (MLVs) obtained were examined by light microscopy and extraliposomal crystals were seen in the preparations from 10.1 and 5.1 mole ratio. One milliliter of the preparations was put in a dialysis bag immersed in 150 ml PBS (closed system) at the physiological pH 7 4 at 37°C Unencapsulated MP at a concentration of 5 mg/ml was used as control. Alternatively, the medium was continuously renewed at a 23 ml/h rate (open system). Serial samples were analysed by HPLC at different times

Results: In the closed system, the release of liposomal MP was controlled by a concentration gradient and reached a plateau after 24 h. while this was achieved after 3 h. with unencapsulated MP In the open system, the clearance of liposomal MP was biphasic and lasted for more than 3 days being dramatically slower than the one of native MP (Table 1).

In vitro-release of liposome-MP (open system), mean ± DS ($n = 3$)

Lipo-MP, mg/ml	Cmax, μg/ml (3–6 h)	C12 h, μg/ml	C24 h, μg/ml	C48 h, μg/ml	C72 h, μg/ml
2	15 8 ± 1 2	6 4 ± 2 4	1 3 ± 0 4	0 05 ± 0 02	0 01 ± 0 01
5	21 9 ± 5 4	13 2 ± 2 4	4 5 ± 1 3	0 4 ± 0 2	0 02 ± 0 01
10	32 1 ± 1 2	21 5 ± 1 1	14 0 ± 2 1	3 5 ± 0 4	0 60 ± 0 5
Native MP (10)	65 3	0 9	0 3		

Conclusions: The experimental data suggested the release of MP from phospholipid bilayers is more sustained as the liposomal MP load is increasing The association-release *in vitro* assays are a reliable method to foresee the *in vivo* behaviour of a liposomal encapsulated drug

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A.430 Effects of melatonin by intrathecal injection. An experimental study in the rat

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Background: Melatonin has been shown to have significant role in the biologic regulation of circadian rhythms, sleep and mood In mans, large doses of melatonin, administrated orally, have a marked short term hypnotic effect. In the light of what is already known about melatonin physiology, we sought to examine the possible therapeutic application of melatonin in anesthesia assessing the hypnotic and antinociceptive effects of a bolus of melatonin, alone or combined with fentanyl, injected intrathecally (IT) or IV in a rat model, and to compare these effects with those produced by fentanyl alone or lidocaine.

Methods: 72 male, Wistar-strain rats, (250–300 gr) divided into 6 groups. in each group of 12 animals, 6 (sub-group A) were studied for the neurological and antinociceptive effects resulting from the substance injected, while breathing room air The remaining 6 (sub-group B) were examined for the possible haemodynamic effects of the substance injected while inhaling 0 6% halothane in oxygen, which sedated them sufficiently to enable haemodynamic monitoring

Injection procedures: (1) 0 08 mg/kg Melatonin (0 02 ml, 0.1%) were injected IT.

(2) IT injection 0 04 mg/kg melatonin (0.01 ml) and of 0.04 mg/kg fentanyl (0 01 ml).

(3) IV injection of 0 08 mg/kg melatonin (0 02 ml, 0 1%)

(4) IT injection of 0.02 ml lidocaine 2% (3 33 mg/kg)

(5) IT injection of 0 08 mg/kg fentanyl (0 005%, 0 02 ml)

(6) 0.6% halothane in 02 but received no IT or IV injection.

Results: Lumbar intrathecal injection of melatonin, 0 08 mg/kg, produced profound sedation and minimal antinocieceptive effect over the lower trunk and hind-limbs of the animals The addition of fentanyl resulted with a greater antinocelceptive effect. IV injection of the same dose of melatonin produced mild sedation.

Melatonin, IT or IV caused a slight reduction in the respiratory rate, with no significant changes in arterial blood gases. A mild decrease in heart rate and systolic blood pressure was also noticed

Conclusions: The clinical applications of these finding will be discussed in details

A.431 Nociceptin inhibits K⁺-evoked glutamate release from rat brainstem slices

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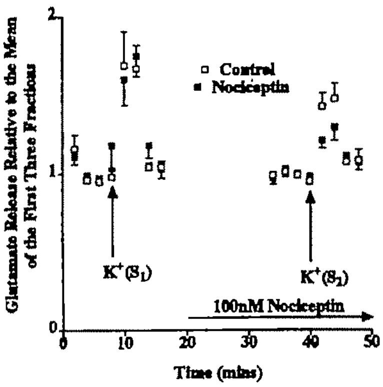
Background & Goal of Study: The orphan opioid receptor, ORL-1 is expressed in the brainstem [1] Nociceptin or orphanin FQ the endogenous ligand for ORL-1 is reported to produce hyperalgesia, analgesia and anti-opioid effects [2]. In an attempt to understand these ions we have examined the effects of nociceptin on K^+-evoked glutamate release from rat brainstem

Materials & Methods: Slices were prepared from Wistar rats and suspended in oxygenated bicarbonate buffer 0 75 ml of gravity packed slices were perfused as described [3] 2 × 2 min pulses of 46 mM K^+ were applied to the slices 30 min apart, S_1 and S_2 respectively 100 nM nociceptin was applied 10 min after S_1 until the end of the experiment. 30 μM amastatin, bestatin, captopril and phosphoramidon and 0.1% BSA were added 10 min after in control and nociceptin treated slices to prevent nociceptin breakdown. Perfusate glutamate concentrations are determined fluorimetrically [3] Data are mean ± sem, S_2/S_1 ratios were calculated from the areas under the S_1 and S_2 curves and analysed by Wilcoxon rank sum test

Results & Discussion: 46 mM K+ depolarisation produced monophasic releases of glutamate during S_1 and S_2, with a an S_2/S_1 ratio for control slices of 1.18 ± 0.11 (n = 7) Nociceptin reduced S_2, thus reducing the S_2/S_1 ratio to 0.71 ± 0.06, an inhibition of ~36%, $p < 0.05$ (Fig 1).



Conclusions: Nociceptin may modulate pain via a reduction in brainstem glutamatergic transmission

Acknowledgements: Financial support is gratefully acknowledged from The Wellcome Trust

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A.432 Prilocaine and lidocaine inhibit (^{3}H)-noradrenaline uptake into 293-hNET cells

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Background & Goal of Study: Intravenous regional guanethidine Bier's block provides a chemical sympathectomy desirable for the relief of reflex sympathetic dystrophy [1]. Local anaesthetic (usually prilocaine or lignocaine) is co-administered to reduce the discomfort caused by noradrenaline displacement We have previously demonstrated that a range of local anaesthetics at clinically achievable concentrations inhibit the uptake of tritiated noradrenaline ([^{3}H]-NA) in SH-SY5Y human neuroblastoma cells and hence would be expected to inhibit the uptake of guanethidine[2, 3]. In this study we have examined the effects of prilocaine and lignocaine on [^{3}H]-NA uptake in cells stably expressing the recombinant uptake$_1$ transporter (293-hNET).

Materials & Methods: 293-hNET cells were maintained in high glucose (4500 mg/l) Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% foetal calf serum, 100 IU/ml penicillin, 100 μg/ml streptomycin, 2 mM L-glutamine and 250 μg/ml geneticin (G418) at 37°C in 5%CO_2/humidified air. Stock cultures were passaged weekly, refed twice weekly and 24 hours prior to any experimental procedure 293-hNET cell suspensions (100–200 μg protein/ml) were preincubated in 0.5 ml volumes of Krebs-HEPES buffer at pH7.4 for >30 mins and <120 mins in the presence or absence of prilocaine and lignocaine (3 μM–100 mM), [^{3}H]-NA (~25 nM) was added and the reaction continued for a further 4 mins. Reactions were terminated by rapid vacuum filtration using a millipore harvester Non-specific uptake was defined in the presence of 10 μM imipramine. The pIC_{50} of prilocaine and lignocaine were estimated by non-linear regression using GRAPHPAD PRISM2. All data are mean ± s.e. mean.

Results & Discussion: 293-hNET cells take up [^{3}H]-NA in a time dependent manner reaching a maximum at 10 minutes. Prilocaine and lignocaine dose dependently inhibited [^{3}H]-NA uptake into 293-hNET cells with pIC_{50} of 3.19 ± 0.05 (644 μM, n = 7) and 2.79 ± 0.11 (1.64 mM, n = 4) respectively. This compares with values of 3.72 ± 0 07 (189 μM, n = 8) and 2.96 ± 0.013 (1.1 mM, n = 4) respectively for SH-SY5Y cells endogenously expressing the uptake$_1$ transporter. [3]

Conclusions: These data with the recombinant uptake$_1$ confirm findings from our previous study with the endogenous NA transporter.

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A.433 Naltrindole-5′-isothiocyanate selectively reverses sufentanil induced respiratory depression in rats

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Background & Goal of Study: Although the cross-interactions between the μ- and the δ-opiate receptor subtypes with regard to supraspinal analgesia are well documented, only a few papers describe the role of the δ-opiate system on μ-opiate induced respiratory depression (1, 2) In order to clarify the functional interactions between both opiate receptor subtypes with regard to antinociception and respiratory depression, rats were intravenously injected with the μ-opiate agonist sufentanil and subsequently intravenously challenged with the delta antagonist naltrindole (NTI) or naltrindole 5′-isothiocyanate (5′-NTII), a δ-2 antagonist

Material & Methods: Approval from the Institutional Animal Care and Use Committee was obtained. Naive male Wistar rats weighing 215–310 g were anaesthetised with etomidate for insertion of an arterial cannulla. After emergence from anaesthesia, the rats were installed in Bolman-cages. The rats were intravenously injected with 2 50 μg/kg of the μ-opiate agonist sufentanil (n = 66) or vehicle (n = 10). Five min after the opioid they were intravenously injected with NTI at 0 16, 0.63, 2 5 and 10 mg/kg or 5′-NTII at 0 16, 0.63, 2.5 and 10 mg/kg. Antinociception was measured by means of the tail flick latency and respiratory depression was evaluated by means of blood gas analysis of PaCO2, PaO2 and oxygen saturation. Statistical analysis included one-way ANOVA, MWU- and Wilcoxon-test.

Results & Discussion: NTI, but not 5′-NTII, antagonized the sufentanil-induced antinociception at doses ≥ 0.63 mg/kg NTI The sufentanil-induced hypercapnia and hypoxia were diminished with 10 00 mg/kg of both NTI and 5′-NTII. Also at 2.50 mg/kg of both antagonists, a short lasting reduction of the respiratory depression was present. These data indicate that 10 mg/kg NTI antagonizes the sufentanil-induced antinociception and respiratory depression in rats, while 10 mg/kg 5′-NTII only reverses the respiratory effects.

Conclusion: With 10 mg/kg 5′-NTII, a dissociation could be obtained between the intravenously sufentanil-induced antinociception and respiratory depression in rats, implying different regulatory mechanisms of the δ-receptor subtypes on the μ-opiate agonist-induced effects.

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A.434 Onset of relaxation after an intubating dose of rocuronium is not accelerated by priming

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Aim: We wanted to evaluate whether priming with rocuronium (R), atracurium (A) or vecuronium (V) accelerated the onset of relaxation after an intubating dose of R. Other relaxants than R as the priming agent were also studied because only R has an early and important presynaptic effect (1)

Method: Four groups of 20 informed and consenting patients each were studied. Anaesthesia was induced and maintained IV with propofol and sufentanil Neuromuscular function was evaluated with acceleromyography using 0.1 Hz stimulation. In a control group (C-R) an intubating dose of 0 6 mg/kg R was injected without priming. In the three other groups a priming dose of 10% of an intubating dose of either R, A or V (group R-R, A-R, V-R) was injected. After a priming interval of 3 minutes the remaining 90% of an intubating dose of R (0.54 mg/kg) was injected. Lag and onset time (the time from injection till achievement of respectively the first signs of relaxation and maximal or total relaxation) were registered.

Results: The median lag and onset times (in seconds) are shown in Table

Table

	C-R	R-R	A-R	V-R
Lag time	30	30	30	25
Onset time	130	200*	150	170

(* p < 0 05 in comparison with the control group)

The onset time was significantly longer in the rocuronium priming group.

Discussion: Priming with either R, A or V does not accelerate the onset of relaxation after an intubating dose with R. The slower onset in the R-R group could be attributed to the lower concentration gradient between plasma and effect site following a 10% lesser intubation dose Griffith et al. observed a significant faster onset time with a similar dosage, a 2 min priming interval and a stimulation frequency of 1 Hz (2) Because R has an early and important presynaptic effect the stimulation frequency of 1 Hz causes fading in the priming group and accelerates the onset. In our opinion priming studies with R must be performed with a stimulation mode which can not cause fading (maximum 0 1 Hz).

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A.435 Influence of induction of anaesthesia on intubation conditions after rocuronium-induced neuromuscular block: comparison of thiopentone and ketamine

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Background and Goal of Study: Intubation conditions are known to be affected by the depth of anesthesia and the drugs used to provide anesthesia The present study was designed to assess the effect of thiopentone (T) and ketamine (K) on intubation conditions after rocuronium-induced neuromuscular block

Methods: After institutional approval, 22 consenting ASA I patients with clinically normal airways, aged 21–44 yr, and undergoing minor elective surgery under general anesthesia were studied Patients were premedicated with 1 mg alprazolam given orally 1 h before surgery and randomly allocated to one of two groups according to the induction of anesthesia. Group T received 2 mg midazolam and 5 mg kg^{-1} thiopentone. Group K received 2 mg midazolam and 2 5 mg kg^{-1} ketamine. Muscle relaxation was provided with rocuronium 0.6 mg kg^{-1}. Tracheal intubation was attempted by an anesthetist blinded as to the allocation, 60 s after rocuronium administration. Intubation conditions were graded as excellent (8–9), good (6–7), fair (3–5), and poor (0–2), on the basis of jaw relaxation, aspect of vocal cords, and response of the diaphragm which were scored from 0 to 3 Neuromuscular transmission was assessed as the response of the adductor pollicis to train-of-four supramaximal stimulation, using a TOF-Guard accelograph monitor. Intubation conditions were compared with the Fischer's exact test and the degree of neuromuscular block was analysed using the Mann-Whitney test $P < 0.05$ was considered statistically significant

Results and Discussion: Both groups were comparable in terms of age, weight and gender distribution. Tracheal intubation was performed within 10 s in all patients. The proportion of excellent intubation conditions was significantly higher in group K (8/11) than in group T (2/11); no significant difference was observed when excellent and good conditions were combined The degree of jaw relaxation did not differ between groups but conditions of vocal cords and diaphragmatic response were significantly better in group K than in group T. The degree of neuromuscular block assessed in both groups at the time of intubation did not differ significantly (T1 response: 46.1 ± 24.4% in group K versus 55 2 ± 22 6% in group T).

Conclusions: The results of the study showed that ketamine provided a significantly higher excellent score of intubation than thiopentone after administration of 0 6 mg kg^{-1} rocuronium This difference was associated with better conditions of vocal cords and diaphragmatic response but could not be ascribed to a deeper degree of neuromuscular block assessed at the adductor pollicis.

A.436 Rocuronium neuromuscular blockade at the masseter and adductor pollicis muscles in adults

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Background & Goal of Study: Rocuronium has a faster onset time at the laryngeal muscles than at the adductor pollicis although the laryngeal muscles have a lower sensitivity to muscle relaxants. This is due to a more rapid equilibration between plasma concentration and that at the laryngeal muscles (1) In this context the rocuronium neuromuscular effect on muscles of the upper airway is an area of some interest. Thus, we evaluated onset and recovery characteristics of rocuronium at the masseter (MM) in comparison to the adductor pollicis muscle (AP).

Materials & Methods: After IRB approval and informed consent, 15 patients were studied. Anaesthesia was induced and maintained with propofol, fentanyl and oxygen/nitrous oxide Neuromuscular responses were monitored with accelerometry (TOF-Guard) Branches of the mandibular nerve were stimulated 1–2 cm anterior to the ear lobe under the zygomatic arch and near the mandibular notch. To measure onset time, supramaximal single twitch stimulation was evoked at 0.1 Hz and, after a stabilization period of 3 min., 0 6 mg/kg rocuronium was injected. Recovery was measured using TOF stimulation every 15 sec until TOF ratio reached 0.85. Statistical analysis were performed with Wilcoxon-test ($p < 0 05$).

Results & Discussion: Onset time was faster at the MM than at the AP Recovery started earlier and time to 25% T_1 recovery was shorter at the AP. No differences were found for times to 50% and 75% T_1 recovery, and for TOF ratio 0.85 (Table 1)

Table 1

	Onset (sec)	Recovery (min)				
		T_{first}	25%	50%	75%	TOF 0.85
AP	93 ± 25	25 ± 5	30 ± 5	35 ± 6	39 ± 7	51 ± 11
MM	48 ± 11	29 ± 6	34 ± 8	38 ± 10	43 ± 11	48 ± 13
p	<0.001	$p < 0 05$	$p < 0 05$	NS	NS	NS

Values are mean ± SD, NS = not significant

Conclusion: We conclude that the rapid rocuronium onset time is a result of the high sensitivity of the MM to muscle relaxants, and the rapid equilibration between plasma and masseter muscle rocuronium concentration Further, we suggest that this higher sensitivity also contributes to a slower initial recovery (2).

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A.437 Evaluation of intense rocuronium neuromuscular block using the post-tetanic counts principle

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Background and Goal of Study: During profound neuromuscular block no response to TOF nervestimulation is seen The post tetanic count (PTC) principle can be used to quantitate the intensity of the block by counting the number of responses following a tetanic stimulation (1). The purpose of this study was to evaluate the relationship between the number of PTC and time to return of the first response to TOF nervestimulation following 3 different doses of rocuronium.

Materials and Methods: After Ethics committee approval and informed consent, 85 patients were included in the study. Anaesthesia was induced with fentanyl followed by thiopentone The patients were randomly given rocuronium 0.6, 0.9 or 1.2 mg/kg. Tracheal intubation was performed at 60 s by a blinded investigator. Intubation conditions were graded using a scoring scheme (2). The neuromuscular block was monitored using TOF stimulation every 12 s and a Myograph 2000. At 6 min intervals, tetanic stimulation (50 Hz) was applied for 5 s preceded and followed by a 30 s period of 1 Hz stimulation until the reappearance of the first response in the TOF nerve stimulation.

Results and Discussion: The intubation conditions were graded as excellent or good in all patients. The first response to TOF was seen 21.6 (5.2), 33 6 (7 3) and 48.7 (13 6) (mean (SD)) min following 0 6, 0.9 and 1.2

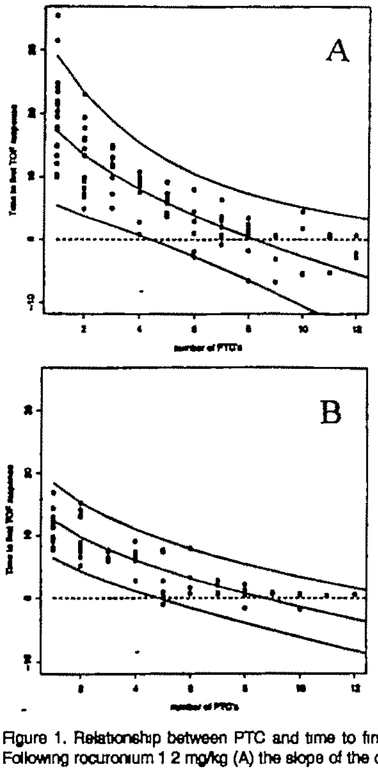

Figure 1. Relationship between PTC and time to first response to TOF stimulation Following rocuronium 1 2 mg/kg (A) the slope of the curve differed from that following 0 6 and 0 9 mg/kg (B)

mg/kg of rocuronium, respectively. A close relationship was found between the time to first response to TOF and the PTC

Conclusion: The PTC principle can be used to predict the time to first response to TOF stimulation during profound rocuronium induced neuromuscular block.

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A.438 Antagonism of rocuronium block in the presence of isoflurane

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Background: Antagonism of neuromuscular block may be impaired in the presence of volatile anaesthetics [1]. We have previously shown that under isoflurane anaesthesia, recovery from rocuronium block is similar when neostigmine 35 or 50 μg kg^{-1} is administered at 10% or 25% recovery [2]. In this study we compared recovery times following neostigmine administration when isoflurane administration was discontinued.

Methods: Forty patients, with their informed consent and Ethics Committee approval, were anaesthetised with thiopentone 4–6 mg kg^{-1}, fentanyl 2 μg kg^{-1} and 67% N_2O in O_2 and isoflurane. After stabilisation of control train-of-four (TOF) responses using mechanomyography, rocuronium 0 5 mg kg^{-1} was given followed by further boluses as required. Isoflurane was discontinued at the end of the procedure and 10 patients each allocated randomly to receive neostigmine 35 (Groups I and II) or 50 μg kg^{-1} (Groups III and IV) at 10 or 25% recovery of T_1 The recovery times of T_1 to 90%, of TOF ratio to 0.8, and the T_1 25–75% were recorded. The data were compared with 40 subjects from the previous study [2] where isoflurane was continued (Groups Ia, IIa, IIIa, IVa). The results were subjected to ANOVA.

Results and Discussion: There was no significant difference in the times to recovery of T_1 to 90% or of the TOF ratio to 0.8, or the interval T_1 25–75% among the groups (Table 1). Our results may indicate that the time during which recovery occurred was not enough for the washout of isoflurane to influence the results. In conclusion, our results indicate that discontinuing isoflurane at the time of administration of neostigmine did not shorten recovery times of rocuronium

Recovery times (min) (n = 10 except a = 9 and b = 8, mean (SD)).

Group	T_1 90%	T_1 25–75%	TOF 0 8
I	5 9 (1 2)	3.1 (1.0)	10 3 (4 3)^a
Ia	6.6 (2 4)^b	3 6 (1 4)^a	8 3 (1 7)^b
II	4 6 (1 0)^b	2.1 (0.7)^b	10.5 (6.2)^a
IIa	6 5 (1 2)^b	3 2 (0 6)	9 5 (4 0)
III	4.5 (2 5)	3 3 (1 8)	7.0 (4 8)
IIIa	4.6 (1 5)^a	3 4 (1 1)^a	6 2 (2 7)^a
IV	4 3 (2 5)	3 1 (2 1)	6 4 (1 9)
IVa	4.0 (1.2)	2 9 (0 7)	5 0 (1 6)^a

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A.439 Pharmacokinetic and pharmacodynamic model of rocuronium in patients undergoing liver transplantation

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The aim of this study is to compare the PK/PD of Rocuronium in healthy adults, normal hepatic function (control group n = 7 (CG)) and in patients with end-stage liver disease, Child's B-C class, (liver transplantation group n = 7 (LT)).

Patients and Methods: Anaesthesia was induced with midazolam, thiopental, fentanyl and maintained with O_2/Air/midazolam and fentanyl as needed. Rocuronium bolus 0.6 mg/kg, Intubation at 60 s, followed continuous infusion was used to obtain blockade level >90%, (start rate 0.5 mg/kg/h). 1 -PD STUDY. the ulnar nerve was stimulated at the wrist with supramaximal TOF and single stimuli, the resultant thumb acceleration measured and recorded on card (TOF-GUARD^R). Lag, latent and onset time and number of changes and mean infusion rate were obtained. 2.-PK STUDY: Plasma (prior to and 1–3–5–10–15–30–60–120–180–240–300 and stop infusion-1–5–10–15–30 min post end infusion), urine (up to 24 h), ascytis and blood losses samples were obtained in each patient. Rocuronium concentration in samples were analysed by HPLC (1). Individual concentration vs effect-time data were fitted to a two exponential equation by means of WIN NONLIN and PKPDFIT programs (2–3). Vss, C1, MRT, t1/2$_\chi$, ke$_0$, t1/2 ke$_0$, γ, EC_{50} and other PK parameters were estimated.

Results:

	Control n = 7	Transplant n =7
Age (years)	46 (16)	48 (15)
Weight (kg)	81 (10)	73 (13)
Surgery time (min)	270 (89)	330 (62)
Infusion time (min)	250 (89)	309 (66)
Nº Inf rate changes	4 5 (1.5)	5 2 (1 7)
Mean infus (mg/kg/h)	0 547 (0 07)	0 617 (0 08)
Lag time (s)	25 7 (11)	34.5 (17)
Latent time (s)	34 (11)	51 (10) *
Onset time (s)	112 (53)	235 (122)
PK variables		
Cl (ml kg^{-1}.min^{-1})	4 8 (1 7)	2 3 (0 5) **
MRT (min)	34 (13)	125 (60) **
Vss (1/kg)	150 (40)	272 (111) **
t 1/2α (min)	2 07 (0 4)	2 20 (2 2)
t 1/2β (min)	29 (10)	97 (48) **
PK/PD variables		
ke$_0$ (min^{-1})	0.287 (0 163)	0 120 (0 014)
t 1/2 ke$_0$ (min)	3 47 (2 03)	6 32 (2.11)
γ	3 69 (1 2)	2 88 (2 27)
EC50 (ng/ml)	766 (323)	1054 (339)

Data as mean (SD) * $p < 0.05$ ** $p < 0\ 01$

Conclusions: In LT patients, rocuronium exert a slightly prolonged effect with a similar onset time (with a large variation) as shown by the NS differences in clinical and PK/PD variables, except latent time The differences in Cl, Vss, t1/2 β and MRT suggest that rocuronium will be present at an effective concentration for a longer period in LT patients The similar rate constant to transfer rocuronium to effect compartment, suggest that the variation in onset is only caused by the increased Vss in LT group. The PK/PD model parameters shown that LT patients need the same plasma concentration to obtain a comparable degree of muscle relaxation as normal patients

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A.440 Chronic carbamazepine therapy and the duration of neuromuscular blockade by rocuronium

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Background and Goal of Study: Patients chronically receiving carbamazepine are known to be resistant to certain, but not all nondepolarizing muscle relaxants (1, 2). Therefore, the influence of carbamazepine on rocuronium-induced NB was investigated in this study.

Materials and Methods: After IRB approval and informed consent, until now a total of 16 patients with ASA physical scores I–III scheduled for neurosurgical procedures were included in the study Only group I (n = 8) patients had received carbamazepine for at least 4 weeks. After induction of anesthesia with thiopental and fentanyl, rocuronium (0.6 mg/kg) was given. Anesthesia was maintained by moderate hyperventilation (Et CO2 at 30–35 mmHg) with N2O 70% and isoflurane 0.5% in O2 Skin temperature was maintained above 36°C. The ulnar nerve was stimulated at the wrist with train-of-four stimuli. Using a Datex NMT monitor, lag time, onset, 10%, 25%, 50%. 75% recovery and the recovery index (RI: 25–75%) were determined. The two tailed t-test for unpaired data and ANOVA was used for statistical analysis $P < 0.05$ was considered statistically significant.

Results and Discussion: Demographic data and measured parameters did not statistically differ between both groups (Table: Mean ± SD in min).

	Carbamazepine	Control	p
Lag time	0 8 ± 0 2	0 9 ± 0 3	NS
Onset	2 4 ± 1 3	2.7 ± 1 0	NS
10% Recovery	19 0 ± 7 6	26 6 ± 10 8	NS
25% Recovery	25 33 ± 8 4	33 5 ± 10 1	NS
50% Recovery	30 3 ± 9.2	40 2 ± 11.8	NS
75% Recovery	36.4 ± 11 4	51.3 ± 15 4	NS
Recovery Index	11 0 ± 4.6	17 8 ± 6.0	NS

Conclusion: Our preliminary results demonstrate that patients on chronic carbamazepine therapy show a shorter duration of rocuronium-induced NB. However, this tendency did not reach statistical significance at this stage of the still ongoing open study. This observation is of special interest as a significant decrease in duration of rocuronium-induced NB was reported in one patient on chronic phenytoin therapy (3). An increased hepatic clearance of the drug seems to be a likely mechanism of this effect.

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A.441 Onset, intubating conditions and duration after mivacurium, rocuronium and their combination in young and elderly adults

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Background: The combination of mivacurium and rocuronium is more potent than each drug given alone, with a fast onset and a short duration of action[1] However, intubating conditions has not been reported with this combination This study was designed to measure neuromuscular block and intubating conditions (INT) of mivacurium, rocuronium, and a combination of both drugs in young and elderly adults.

Methods: After informed consent, two groups of 45 patients scheduled for elective surgery under general anesthesia requiring tracheal intubation were enrolled into the study. Patients aged 18–65 yr. were enrolled in group Young (Y), and those aged 66–90 were in group Elderly (E) Patients were randomized to receive mivacurium, 0.25 mg kg^{-1}, or mivacurium, 0.08 mg.kg^{-1} plus rocuronium, 0.2 mg.kg^{-1}, or rocuronium, 0.6 mg.kg^{-1} The trachea was intubated 2.5 min after the injection of the relaxant The response of the adductor pollicis was measured with accelerometry. The response of the orbicularis occuli (OO) was estimated visually Intubating conditions were rated by an observer blind to the study. No significant differences were found between the relaxants given with respect to onset at AP, onset at OO and (INT) For statistical analysis one way ANOVA and Kruskall-Wallis ANOVA was used as appropriate.

Results: Onset and intubating conditions were similar in the Y and in the E. In the Y group, recovery was longer in the rocuronium subgroup than in either the mivacurium or combination subgroups In the E group, recovery was shortest with mivacurium, intermediate with the combination and longest with rocuronium.

	Group Y (n = 45)		
	MIV (n = 14)	COM (n = 18)	ROC (n = 13)
Onset AP, sec (mean ± SD)	271 ± 103	276 ± 102	253 ± 132
Onset OO, sec (mean ± SD)	142 ± 54	151 ± 49	158 ± 67
Dur 25%, min (mean ± SD)	23 ± 6	25 ± 7	39 ± 11*
INT (1/2/34)	7/6/2/0	8/7/0/0	10/5/0/0

	Group E (n = 45)		
	MIV (n = 15)	COM (n = 15)	ROC (n = 15)
Onset AP, sec (mean ± SD)	239 ± 115	276 ± 102	253 ± 132
Onset OO, sec (mean ± SD)	158 ± 75	173 ± 62	184 ± 110
Dur 25%, min (mean ± SD)	24 ± 6	35 ± 11*	54 ± 11*
INT (1/2/34)	11/4/0/0	11/4/0/0	13/2/0/0

*P < 0.05

Conclusions: This study suggests that, in adults of all ages the combination of rocuronium and mivacurium yields onset times and intubation conditions at 2.5 min similar to those obtained with either drug used alone, but by using only 2/3 as much total drug. Thus, mivacurium-rocuronium combination can be used in short procedures as an alternative to mivacurium

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A.442 Pharmacodynamics and tryptase release of rocuronium and cis-atracurium in anaesthetised patients

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Background and Goal of the Study: Rocuronium (R) and Cis-atracurium (CA) are two non-depolarizing muscle relaxants with an intermediate duration of action (1, 2). The aim of this study was to compare the intubating conditions, pharmacodynamics and tryptase release after the administration of this two muscle relaxants.

Patients and Methods: Forty ASA I or II surgical patients were studied. Patients were randomized into two groups (group CA and group R) of 20 patients each Premedication consisted of droperidol (2.5–5 mg) and fentanyl (0.05–0.10 mg) IV before induction. Anaesthesia was induced using thiopental (5 mg/kg) and fentanyl (0.10–0.15 mg) Neuromuscular transmission was monitored using a TOF-Guard monitor (Biometer) The group CA received a bolus of 0.15 mg/kg and the group R a bolus of 0.6 mg/kg to facilitate tracheal intubation Intubating conditions were evaluated at 1 min (group R-1), 1.5 min (groups R-2 and CA-1) and 2 min (group CA-2). Intubating conditions were evaluated as excellent, good, fair or bad. Anaesthesia was maintained with nitrous oxide 65% in oxygen and fentanyl as required An infusion at a starting rate of 0.09 mg/kg/h (group CA) and 0.5 mg/kg/h (group R) was administered after recovery 5% of control The infusion rate was changed to maintain 90% twitch depression. The following pharmacodynamic parameters were studied Time to 25% and 95% depression of twitch height (TD25%, TD95%), recovery time 25–75% (RT), infusion rate (IR), and intubation twitch (ITw) Blood samples analysed for Tryptase concentrations were taken at regular intervals (baseline, 60 and 120 min) The results are presented as mean ± SD Statistical analysis was performed using Student's t-tests ($p < 0.05$ was considered significant)

Results:

	Group CA	Group R	
TD25% (sec)	100.5 ± 37	44.2 ± 16.5	p < 0.001
TD95% (sec)	263.7 ± 55.4	174 ± 51.3	p < 0.001
RT 25–75% (min)	10.8 ± 3.2	14.5 ± 4.3	p < 0.05
IR (mg/kg/h)	0.093 ± 0.009	0.56 ± 0.10	
ITw (%)	63.05 ± 28.3	30.7 ± 20.9	p < 0.001

Group/Intubating Conditions (n)	E	G	F	B
CA-1 (1.5 min)	1	8	1	–
CA-2 (2 min)	8	2	–	–
R-1 (1 min)	5	5	–	–
R-2 (1.5 min)	9	1	–	–

Conclusion: R may be an alternative to suxamethonium for rapid sequence induction R and CA do not induce significant Tryptase release

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A.443 Mivacurium neuromuscular effects in elderly *vs* adult patients

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Mivacurium is a short-acting nondepolarizing relaxant that is hidrolyzed by plasma cholinesterase We have compared the neuromuscular blocking properties in very old vs adult patients We have also examined the relationship of the duration of action to the plasma cholinesterases levels and the incidence of coughing and flushing

Methods: We included 40 adult (35 ± 16 yr) and 40 elderly patients (82 ± 14 yr), ASA I–II, undergoing elective orthopaedic surgery They were anesthetized with propofol, fentanyl and 60% N_2O in O_2 with 0.5–1% isoflurane Neuromuscular transmission was monitored by evoked adductor pollicis EMG (train-of-four stimuli at 10 sec intervals; Relaxograph™, Datex). Following a stable EMG response, a mivacurium bolus dose 0.2 mg/K (3 x DE_{95}) was given over 15 sec The data recorded were lag time (from injection to first decrease in T_1), latent time (time to 25% decrease in T_1), onset time (time to maximum block), clinical duration (time from injection to return of T_1 to 25% of control), recovery index (RI), time to recovery of TOF ratio to 0.7 (TOF 0.7) and the presence of flushing and coughing at intubation time (all of them with $T_1 < 5\%$) Data were analyzed by two tail t-test, ANOVA and Fisher's exact test ($p < 0.05$ vas considered significant).

Results: Table I shows no different onset characteristics in both groups, while recovery times, except RI, were significantly ($p < 0.001$) higher in elderly group. There was no correlation between recovery times and plasma cholinesterases levels when these were in normal range (3000–9000 U/L) although longest durations were with less than 3000 U/L. We have also seen high incidence of coughing, without difference in both groups, instead of very good intubating conditions, and significant higher incidence of flushing in adult patients ($p < 0.001$)

Neuromuscular data (mean ± SD)

	Onset*	T_1 25%**	RI	TOF 0.7**
Adult	192 ± 23 s	16 ± 7 min	8 ± 2 min	28 ± 7 min
Elderly	180 ± 34 s	27 ± 11 min	10 ± 5 min	41 ± 17 min

(* $p < 0.02$) (** $p < 0.01$)

Discussion: As in other studies, our results show longer (60%) clinical duration of mivacurium in elderly. The rather poor correlation of plasma cholinesterases levels with recovery times suggest the existence of other routes of metabolism. Finally, we think is necessary an objective neuromuscular monitoring method because of the high variability of recovery times in both groups

A.444 Assessment of intubating conditions in adults after induction with propofol and varying doses of remifentanil

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Background & Goal of Study: Previous work in adults showed that tracheal intubation could be successfully achieved following induction of anaesthesia with alfentanil and propofol without the use of muscle relaxants. Given the pharmacokinetic profile of remifentanil it was hypothesized that it may be used in this application

Materials & Methods: In a prospective randomised double-blind trial, 60 ASA I–II patients with favourable airway anatomy were studied in 3 groups All patients were premedicated with temazepam 30 mg and ranitidine 150 mg Intubating conditions and the patients haemodynamic response to intubation were assessed pre-induction, post-induction and post-intubation with propofol 2 mgkg^{-1} and remifentanil 0 5, 1.0 or 2.0 μgkg^{-1}. Remifentanil was administered as a slow bolus over 30 seconds. Tracheal intubation was graded according to the ease of laryngoscopy, position of the vocal cords, coughing, jaw relaxation and movement of the limbs Parametric data was analysed using ANOVA. χ^2 analysis was applied to non-parametric data. $P < 0\ 05$ was regarded as significant

Results & Discussion: Intubation was successful in 80%, 90% and 100% of patients after remifentanil 0.5, 1.0 or 2 0 μgkg^{-1} respectively. Overall intubation conditions were regarded as excellent in 20%, 50% and in 80% of patients respectively with a significant difference between groups ($P < 0\ 05$). Blood pressure dropped in all 3 groups post-induction but not significantly No patients developed chest wall rigidity or a bradycardia The results presented here compare favourably with equally potent doses of alfentanil combined with propofol for intubation (1). Alfentanil has very variable metabolism (2) This may lead to apnoea when it is used to facilitate intubation of the trachea Remifentanil has a context-sensitive half-life of approximately 3 min. The short duration of action of may confer an advantage when used in tracheal intubation

Conclusion: Adequate conditions for laryngoscopy and intubation of the trachea were produced in premedicated adults following induction of anaesthesia with remifentanil 2.0 μgkg^{-1} as a slow bolus over 30 seconds, followed by propofol 2 mgkg^{-1}. Conditions with this dose were better than those obtained with remifentanil 0.5 or 1.0 μgkg^{-1}.

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A.445 Comparison of three doses of remifentanil for intubation with no muscle relaxation in adults

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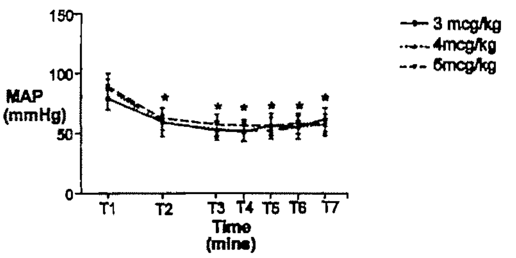
Background and Goal: Intubation without the use of muscle relaxants has been described[1] Remifentanil is a new opioid with a rapid onset of action and rapid clearance with short lived side effects[2] The hypothesis was to determine the dose of remifentanil required for good intubating conditions when administered with propofol.

Materials and Method: With IRB approval and informed written consent, 33 ASA 1 or 2 patients undergoing general anaesthesia with elective tracheal intubation were studied All patients were premedicated with midazolam 0.03 mg kg^{-1} iv. Routine monitoring was instituted and the patient preoxygented. Each patient was randomly allocated to one of three groups; remifentanil 3 mcg kg^{-1} iv (group A), 4 mcgkg^{-1} (group B) or 5 mcg kg^{-1} (group C) which was administered immediately after propofol induction (2 mg kg^{-1}). After one minute the patient was intubated by an anaesthetist blinded to the study drug and the conditions of intubation were scored as: 0) unable to intubate, 1) poor, 2) fair, 3) good and 4) excellent. Haemodynamic parameters were measured before induction (T 1), before intubation (T 2) and for every minute (T 3–7) after intubation for five minutes Ephedrine was given if the systolic blood pressure fell below 65 mmHg. Statistical analysis utilized SAS software and included shapiro-wilk test for normality, t-test or wilcoxon sign rank test as appropriate for nominal data, and chi-square test for categorical data.



Results: There was no difference in demographic data between the groups. The number of patients with good or excellent intubating conditions were: group A, 5* (n = 9); group B, 11 (n = 11); and Group C, 3 (n = 13); *$p < 0.0013$. Mean arterial pressure ± SEM is shown (fig., * $p < 0\ 05$).

Conclusion: Remifentanil 4 mcg kg^{-1} provides excellent intubating conditions compared with 3 mcg·kg^{-1} while associated with similar decreases in mean arterial pressure (37–40% decrease from pre-induction values).

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A.446 Use of remifentanil to prevent a rise in intraocular pressure following suxamethonium and intubation

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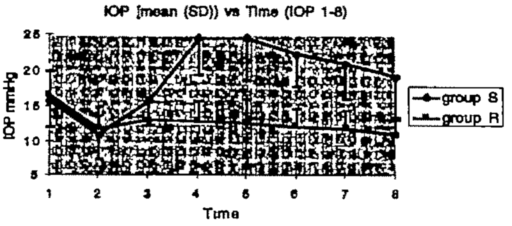
Background and Goal: Suxamethonium and tracheal intubation increase intraocular pressure (IOP)[1] Remifentanil is a new potent opioid with a rapid onset of action and rapid clearance with short lived side effects[2]. We have compared the use of remifentanil with placebo to attenuate the rise in IOP following suxamethonium and tracheal intubation

Materials and Method: With IRB approval and informed written consent, 20 adults (ASA 1 and 2) undergoing elective eye surgery were studied They were premedicated with midazolam 0 03 mg kg^{-1} iv 10 minutes before anaesthesia. Routine monitoring was instituted and the patient preoxygented ·Each patient was randomly allocated to receive remifentanil 1 mcg kg^{-1} (group R) or saline (group S) Anesthesia was induced with propofol 2.0 mg kg^{-1} and the study drug was given immediately before suxamethonium 1 mg kg^{-1}. After one minute the patient was intubated by an anaesthetist blinded to the study drug. The patient was ventilated to normocapnia and anaesthesia maintained with isoflurane 1% and nitrous oxide 70% in oxygen. Intraocular pressure was measured in the unoperated eye immediately before induction (IOP 1, before study drug administration (IOP 2), before intubation (IOP 3) and every minute for five minutes (IOP 4–8) using a Tono-Pen by one of the authors (WJL) also blinded to the study preparation. Wilcoxon rank sum test was used for comparison of IOP and student T-Test for demographic analysis.

Results: Mean age was significantly different between groups R and S (45.8 yr SD ± 15 1 vs 59.7 ± 12 6 respectively) $P < 0\ 05$ There was a significant fall in mean IOP for both groups from IOP 1 to 2 ($P = 0.016$). The IOP rose significantly after administration of suxamethonium (IOP 3) ($P < 0.05$) and intubation (IOP 4–8) in group S compared with group R ($P < 0.001$)



Conclusion: Remifentanil 1 mcg kg^{-1} bolus attenuates the rise in IOP after administration of suxamethonium and tracheal intubation following propofol induction

References

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A.447 Rational alfentanil administration improves haemodynamic stability during direct laryngoscopy under TIVA

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Background: Direct laryngoscopy is a strong, brief noxious stimulus that may induce dangerous hypertension Opioids are added to propofol anaesthesia to limit this response. The goal of this study was to optimise alfentanil dosing scheme[1] in order to improve haemodynamic stability without additional side effects as hypotension or late recovery

Methods: Over a 6 months period, 2 groups of patients scheduled for direct laryngoscopy were studied. All received propofol (2.5 mg/kg then 10 mg/kg/h) and high frequency jet ventilation via intercricothyroid catheter (without intubation).

The first group (n = 19) received as usually in our hospital a single alfentanil iv bolus of 10 μg/kg, resulting in a predicted alfentanil plasma concentration ~50 ng/ml (Stanpump, Dr SL Shafer, Stanford) at the beginning of laryngoscopy. Then, the concentration fell dramatically in the next minutes.

In the second group of patients (n = 23), the alfentanil dose was designed in order to maintain a concentration ~50 ng/ml during the whole laryngoscopy The bolus was decreased to 6 μg/kg followed by an infusion of 0.8 μg/kg/min. Incidence of hypotension (SBP < 80 mmHg)[2] and hypertension (SBP > 160 mmHg) were compared between the 2 groups by c^2. Total doses of drugs (including the initial bolus) and delay to recovery were compared by t-test.

Results: The 2 groups were similar regarding to weight, age, duration of anesthesia, total dose of propofol and incidence of hypotension after induction, before laryngoscopy. Incidence of hypertension during laryngoscopy was significantly decreased when alfentanil was given as bolus + infusion (group 2)

Mean values	Group 1	Group 2
Duration of procedure (min)	18.8	16 1
Hypotension prior to laryngoscopy	2/19	3/23
Total alfentanil (μg/kg/min)	0.65	1.06 *
Total propofol (mg/kg/h)	19.1	21 9
Hypertension during laryngoscopy	8/19	3/23 *
Time to spontaneous ventilation (min)	7 1	5 9
Time to respond to command (min)	10 9	8 8

* $p < 0\ 05$, group 2 *vs* group 1

Discussion: Modifying the alfentanil dose scheme in order to maintain a stable plasma concentration during laryngoscopy decreases the incidence of hypertension when compared to a single iv bolus. It requires a lower bolus but a higher total dose of alfentanil This dose increase had no consequence neither on hypotension before nor on respiratory depression after the laryngoscopy. We conclude that such a bolus + infusion scheme could be recommended to improve safely haemodynamic stability during direct laryngoscopy.

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A.448 Predictive performance of a population pharmacokinetic data set of remifentanil in target-controlled infusion

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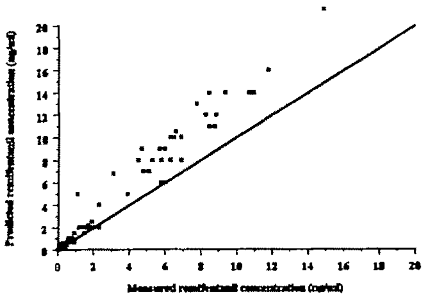
Background & Goal of the Study: The pharmacokinetics of remifentanil (REM) make it suitable for target controlled infusion (TCI). We studied the predictive performance of a TCI device when provided with a population pharmacokinetic data set of REM[1]

Materials and Methods: With ethics committee approval and informed consent, 6 ASA 1–2 female patients undergoing lower abdominal surgery received a TCI of REM and propofol (PROP). The target PROP concentration was maintained constant at 2–6 μg/ml, whereas the target remifentanil concentration was varied according to patient responses. Arterial blood samples were taken frequently for determination of the blood REM concentration The predictive performance was determined on the basis of the performance error[2], that was calculated as $((C_m - C_p)/C_p)^* 100$, where C_m and C_p are the measured and predicted REM concentrations Subsequently, the bias and inaccuracy were assessed as the median (MDPE) and the median absolute (MDAPE) performance error.,

Results and Discussion: A total of 91 arterial blood samples were analyzed. The MDPE and the MDAPE of the REM pharmacokinetic data set were −27% and 25%. Because the 95% confidence interval of MDPE (−30 4%—21 5%) did not include 0, it was concluded that a significant bias had occurred



Conclusions: The use of a population pharmacokinetic parameter set of REM in TCI during PROP anaesthesia results in a significant overprediction of the measured blood remifentanil concentrations

References

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A.449 A prospective, randomized comparison of recovery times after remifentanil/propofol/oxygen, remifentanil/desflurane/oxygen, remifentanil/sevoflurane/oxygen and alfentanil/isoflurane/nitrous oxide anaesthesia for ENT surgery

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Background and Goal of Study: The pharmacokinetics of remifentanil (REM), desflurane (DES), and sevoflurane (SEV) make them highly attractive for ENT-surgery Accordingly, this study was to compare recovery times following REM/propofol (PRO), REM/DES, REM/SEV and alfentanil/isoflurane/N_2O/O_2 (control [CONTR]) anaesthesia

Materials and Methods: Following approval by the local Ethics Committee and written informed consent, 120 patients were randomly assigned to either REM/PRO, REM/DES, REM/SEV or CONTR anaesthesia (n = 30 each). Times from discontinuation of anaesthesia until return of spontaneous respiration, eye opening, and extubation, and from the time of extubation to statement of name and date of birth were determined Data were statistically analyzed by Kruskal-Wallis test, Mann-Whitney rank sum test and χ^2-analysis (significance level $p < 0.05$)

Results (Table) and Discussion: Patient characteristics were comparable between groups Compared to the REM groups, time intervals until extubation and statement of name and date of birth were considerably longer in the control group In the REM groups, return of spontaneous respiration, eye opening and extubation occurred almost simultaneously

Recovery characteristics (min)

	REM/PRO	REM/DES	REM/SEV	CONTR
Duration of anaesthesia				
	115 (48–286)	113 (57–353)	116 (74–332)	115 (48–188)
Time intervals from discontinuation of anaesthesia until				
Spont breathing	6 3 (2–11)	5 0 (1–11)	4 8 (1–10)	5 8 (0–17)
Eye opening	5 7 (1–11)	4 7 (1–11)	4 6 (1–10)	9 4 (3–23)*
Extubation	6 7 (2–13)	5 2 (1–11)	5 2 (2–10)	8 1 (3–24)*
Time intervals from extubation until statement of .				
Name	1 7 (1–8)	1 4 (1–4)	1 5 (1–4)	7 5 (1–29)*
Date of birth	1 7 (1–8)	1 4 (1–4)	1 5 (1–4)	7 9 (1–29)*

Values are means (range) *$p < 0\ 05$ vs other groups

Conclusion: Although the faster extubation in the REM groups may be of marginal clinical relevance (1.5–3 min difference), extubation in the REM groups was performed in much more responsive patients (as indicated by simultaneous eye opening and almost immediate statement of name and date of birth after extubation). This conveys an additional factor of safety and accelerates discharge of the patient from the operating room

A.450 A prospective, randomized comparison of postoperative patient comfort and satisfaction after remifentanil propofol/oxygen, remifentanil/desflurane/oxygen, remifentanil/sevoflurane/oxygen and alfentanil/isoflurane/nitrous oxide anaesthesia for ENT surgery

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Background and Goal of Study: The pharmacokinetics of remifentanil (REM), desflurane (DES), and sevoflurane (SEV) make them highly attractive for ENT-surgery Accordingly, this study was to evaluate patient comfort and satisfaction following REM/propofol (PRO), REM/DES, REM/SEV and alfentanil/isoflurane/N_2O/O_2 (control[CONTR]) anaesthesia.

Materials and Methods: Following approval by the local Ethics Committee, 120 patients were randomly assigned to either REM/PRO, REM/DES, REM/SEV or CONTR anaesthesia (n = 30 each). Visual analog scores (VAS, 0[best]–10[worst]) for pain, nausea and sleepiness were evaluated at 30 and 90 min, and 4 and 24 h, and VAS for patient satisfaction at 48 h post extubation Data were analyzed by Kruskal-Wallis and Mann-Whitney rank sum test (significance level $p < 0\ 05$)

Results (Table) and Discussion: Patient characteristics were comparable between groups. At 30 and 90 min, nausea-VAS was lower following

REM/PRO, and sleepiness-VAS higher following CONTR compared to the other groups. Satisfaction-VAS were comparable between groups.

Visual analog scores (VAS) (0 [best]–10 [worst])

	REM/PRO	REM/DES	REM/SEV	CONTR
Pain-VAS				
30 min	2.6 (0–7.2)	3.5 (0–7.0)	3.3 (0–8.3)	3.2 (0–8.5)
90 min	2.1 (0–4.9)	2.5 (0–7.1)	2.1 (0–7.9)	2.8 (0–8.4)
4 h	1.4 (0–8.9)	1.6 (0–5.7)	1.7 (0–9.2)	1.6 (0–4.9)
24 h	1.4 (0–4.9)	1.0 (0–6.6)	0.8 (0–5.7)	1.3 (0–6.9)
Nausea-VAS				
30 min	0.2 (0–2.1)*	1.7 (0–5.1)	1.5 (0–7.2)	2.0 (0–6.7)
90 min	0.1 (0–1.5)*	1.5 (0–7.5)	1.2 (0–7.3)	1.3 (0–7.3)
4 h	0.6 (0–4.7)	0.8 (0–6.4)	0.6 (0–3.8)	0.6 (0–7.2)
24 h	0.2 (0–3.1)	0	0.1 (0–1.3)	0.3 (0–3.3)
Sleepiness-VAS				
30 min	3.2 (0–9.1)	3.4 (0–6.6)	3.4 (0–8.3)	4.9 (0.8–9.0)*
90 min	2.4 (0–10)	2.4 (0–6.0)	1.8 (0–9.1)	3.0 (0–9.1)*
4 h	1.2 (0–6.1)	1.5 (0–5.8)	1.5 (0–6.3)	1.4 (0–10)
24 h	0.8 (0–9.4)	0.3 (0–5.0)	0.3 (0–2.6)	0.8 (0–6.6)
Satisfaction-VAS				
	0.6 (0–5.4)	1.1 (0–10)	0.5 (0–3.6)	0.6 (0–6.9)

Values are means (range) *$p < 0.05$ vs other groups

Conclusion: Our results indicate less nausea following REM/PRO, and faster recovery of alertness following all REM-based anaesthetics in the early postoperative period. Patients appear equally satisfied with all four anaesthetic regimens.

A.451 Effect of premedicated oral ketamine on reducing the pain both on injection of propofol and on placing the venous catheter

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Introduction: To reduce the incidence of pain on injection of propofol we studied the effects of pretreatment by 0.2 mg/kg ketamine intravenously and showed that it provides satisfactory pain relief. We, however, supposed that premedicated ketamine may reduce the pain when inserting venous catheter as well. We, therefore, studied a double-blind comparison of premedicated oral ketamine and a placebo of the incidence of pain both on injection of propofol and on insertion of a venous catheter.

Methods:

After acquiring Institutional Ethical Committee clearance and informed consent, 48 (ASA 1 or 2) patients scheduled for ENT surgery were studied. Patients were randomly assigned to receive either only 5 ml syrup (group S, n = 24) or 2 mg/kg ketamine in syrup (group KS, n = 24) on a double-blind bases one hour prior to anaesthesia induction. Upon arrival in the operating room, a 20 G catheter was placed in the largest vein of the non-dominant hand or forearm Patients were asked to assess the severity of pain from 0 for none to 3 for severe. Anaesthesia was induced with 2 mg/kg propofol at the rate of 300 ml/h and patients were asked if they had a stinging feeling in their arms. On the day after operation patients were also asked if they could recall the venous catheter and if they had memory of pain in the arms during the induction of anaesthesia.

Results: The patients in group KS were well sedated before induction. The pain on placing the catheter was significantly lower in group KS (median 1.5, range 0–3) than in group S (median 2, range 1–2) In group KS 83.3% of the patients had no pain on infusion of propofol, as did 25% in group S. Patients who could not recall having catheter and pain on infusion were 75% and 66.7% in group KS and 16.7% and 12.5% in group S.

Discussion: The statistically significant difference in number of the patients who had pain on receiving the venous catheter and on injection of propofol between Group S and Group KS suggests that premedicated oral ketamine provides satisfactory pain relief for both. Most patients in Group K did not recall the venous catheter regardless of the level of pain on insertion or their level of consciousness, this may be helpful in allowing patients to overcome a difficult operation.

Conclusion: When combined with an adequate level of sedation orally premedicated 2 mg/kg ketamine is a good method as it provides satisfactory pain relief not only during injection of propofol but also when inserting a venous catheter.

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A.452

ABSTRACT WITHDRAWN

A.453

ABSTRACT WITHDRAWN

A.454 Low-dose droperidol (0.625 mg, 1.25 mg and 2.5 mg) has no effect on postoperative anxiety, restlessness and overall mood

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Background: Droperidol (D) in low doses such as 1 25 mg [1] or even 1 mg and 0 5 mg [2] can increase anxiety and restlessness in the postoperative period. The aim of this study was to determinate whether these side effects indeed occur frequently following low-dose D and to see if this is dose related.

Methods: 184 female patients ASA grade 1 and 2 undergoing gynaecological laparoscopy were recruited to this prospective, double-blinded study. General anaesthesia was performed in a standardized manner (induction with thiopentone, fentanyl 2μg/kg and vecuronium 0 1 mg/kg, tracheal intubation, maintenance with enflurane in N_2O/O_2). Patients were randomly allocated to receive saline (n = 45), D 0.625 mg (n = 47), D 1.25 mg (n = 46) or D 2.5 mg (n = 46) i v 10 minutes before the end of surgery. Preoperatively, and 1, 3, 6, and 24 hours postoperatively, the patients' anxiety, restlessness, and overall mood was evaluated using two psychological questionnaires (Erlanger anxiety and tension-scale/BSK-test). Sedation was evaluated by a subtest of the BSK-test. Statistical analysis was performed using the Kruskal-Wallis and the Wilcoxon-test as a posthoc test. Furthermore, postoperative nausea and vomiting (PONV) was assessed with a 100 mm visual analogic scale and by counting the episodes of retching and vomiting. PONV was then rated as none, mild, moderate or severe using a fixed scoring algorithm. The χ^2-test was used for statistical analysis

Results: All groups were comparable for biometric data, duration of surgery and anaesthesia and possible risk factors for PONV

The scores for anxiety, restlessness and overall mood were not significantly different between the groups at any observation time Quality of sleep in the first night after surgery was the same in all groups. Only the sedation scores were significantly different 1 h (p = 0.011) and 3 h (p = 0.011) postoperatively in a dose-dependant manner, but duration of stay in the recovery room did not differ.

Compared to placebo, PONV was significantly reduced by D (p = 0 012, see table)

PONV	Placebo	0 625 mg	1 25 mg	2 5 mg
None	42 2%	70 2%	54 3%	73 9%
Mild	22 2%	10.7%	8 7%	17 5%
Moderate	15 6%	10 6%	15.3%	2 1%
Severe	20%	8 5%	21 7%	6 5%

Conclusion: Droperidol is an effective antiemetic drug and it does not influence postoperative anxiety, restlessness and overall mood in female patients undergoing gynaecological laparoscopy

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A.455 Dimenhydrinate reduces the incidence of postoperative nausea and vomiting in female inpatients

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Background: Dimenhydrinate (D) is an inexpensive antihistaminic drug, that is frequently used as an antiemetic in anaesthesia [1] The popularity of the drug is contrasted by the lack of modern studies concerning its efficacy in reducing the incidence of PONV [2]. Thus, dimenhydrinate was compared to placebo (P) in a prospective, randomized, double-blind study.

Methods: 133 female inpatients undergoing orthopaedic surgery were studied. General anaesthesia was induced with etomidate, fentanyl (2 μg/kg), vecuronium, and maintained with enflurane in N_2O/O_2 Neuromuscular block was reversed with pyridostigmine/atropine in all patients. Patients in the D-group (n = 67) received 62 mg dimenhydrinate i v. after induction of anaesthesia. P-patients (n = 66) received saline. Administration of dimenhydrinate (and placebo) was repeated three times postoperatively over a period of 24 hours to ensure constant plama levels of the drug, due to its short half life Postoperative analgesia was achieved by metamizole, diclofenac and piritramid on demand Patients were observed over a 48 hour period postoperatively Episodes of vomiting, reaching and need for additional antiemetics were recorded. Nausea was assessed using a 100 mm visual analog scale (VAS). PONV was rated as "none", "mild", "moderate", and "severe" using a fixed scoring-algorithm. Statistical analysis was performed using the χ^2-test

Results: There were no differences between the two groups with regard to biometric data, type of surgery, history of PONV or motion sickness In the D-group the incidence of PONV was significantly reduced compared to placebo (see table, p = 0 0024) The incidence of side effects (dry mouth, blurred vision) was the same in both groups

Severity of PONV	Dimenhydrinate	Placebo
None	26 (38 8%)	10 (15 1%)
Mild	13 (19 4%)	11 (16 7%)
Moderate	18 (26 9%)	19 (28 8%)
Severe	10 (14 9%)	26 (39 4%)

Conclusion: Dimenhydrinate is a safe and effective antiemetic in female inpatients, when its administration is repeated 3 times postoperatively over a period of 24 hours.

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A.456 Sevoflurane does not reduce postoperative nausea and vomiting compared with enflurane and isoflurane

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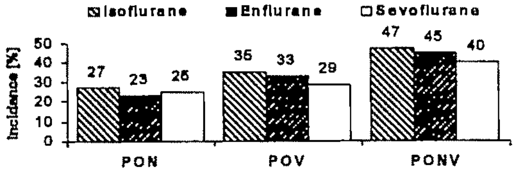
Background: Postoperative sequelae such as nausea (PON), vomiting (POV) and nausea and vomiting (PONV) still frequently occur after ENT- and squint-surgery. Maintenance of general anaesthesia with sevoflurane is thought to reduce the incidence of PONV (1) Therefore we evaluated the efficacy of sevoflurane in order to reduce PONV in patients with increased risk according to a previously developed risk score (2)

Materials and Methods: With approval of the local ethics committee and written informed consent 657 ASA 1 to 3 patients scheduled for elective ENT- and strabismus-surgery were randomly assigned to one of three groups Standardized general anaesthesia was stratified After induction with thiopentone patients received isoflurane (group 1, n = 236), enflurane (group 2; n = 239) or sevoflurane (group 3, n = 182) in N_2O/O_2 2:1. Due to stratification the allocation of opioids (equianalgesic doses of fentanyl, alfentanil and sufentanil) and antiemetics (droperidol, dimenhydrinate, tropisetron and metoclopramide) were similar for all groups. Emetic episodes as well as nausea were recorded over 24 hrs according to a standardized protocol. Statistical analysis were performed using the chi-square test with p < 0 05 considered as statistically significant and power analysis revealed a minimum of 174 patients for a calculated reduction from 30 to 15% (α = 0.05 and β = 0 1).

Results: There were no significant differences among the groups with regard to patient demographics and surgical procedures There was no statistical difference as regards the incidence of emetic symptoms (PON, POV and PONV) between group 3 (25%, 29% and 40%) compared to group 1 (27%, 35% and 47%) and group 2 (23%, 33% and 45%) respectively



Conclusion: The data suggest that with respect to emetic sequelae sevoflurane fails to show any beneficial effect compared to enflurane and isoflurane.

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A.457 Comparative study of the effect of desflurane with nitrous oxide *vs* desflurane without nitrous oxide on postoperative nausea and vomiting in female patients undergoing breast surgery

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Background & Goal of Study: A recent meta-analysis showed that omitting N2O significantly reduced postoperative nausea and vomiting (PONV) compared with a N2O regime (1) Our study was designed to evaluate the effect of the combination of desflurane with N2O versus desflurane alone on PONV in a subgroup of female patients and PONV was considered as the primary endpoint (2).

Materials & Methods: After approval of the local ethics committee and informed consent 60 female patients (ASA 1&2), aged 18–65 y, and scheduled for breast surgery with a duration of 1–3 h were included. Obese patients or patients with a history of PONV and motion sickness were excluded No prophylactic anti-emetic therapy was allowed during the study Patients received a standardized anaesthetic technique consisting of propofol for induction, vecuronium and fentanyl for intubation, followed by desflurane with or without N2O (randomisation list) and fentanyl supplements if required for maintenance of anaesthesia. At the end of anaesthesia PONV was recorded during 24 h in different periods Data of incidence and severity of PONV and use of rescue medication were gathered at the end of each period Statistical evaluation was performed using t-test, chi-square test or Cox log rank test and $p < 0.05$ was considered significant

Results: There were no significant differences between the groups with respect to demographic data and duration of anesthesia. In addition, there were no significant differences in the amount of intraoperative fentanyl or postoperative narcotics. The incidence of PONV was significantly higher in the group of patients receiving desflurane in N2O-O2 mixture compared with the group receiving desflurane in AIR-O2 mixture (table 1)

	Group N2O (n = 30)	Group No N2O (n = 30)	Statistical Signifance
PONV	17	6	p = 0.0035
Nausea	17	5	p = 0.0013
Vomiting	12	5	p = 0.0449
Rescue	15	5	p < 0.005

Conclusion: The combination of desflurane with N2O in female patients undergoing breast surgery is associated with a significantly higher incidence of PONV and a higher need of antiemetic drugs.

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A.458 Ondansetron is more effective than metoclopramide in the treatment of opioid-induced emesis in post-surgical adult patients

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Background and Goals: Nausea and vomiting are common side-effects of opioids given for pain control This study evaluated the efficacy and safety of ondansetron and metoclopramide in the treatment of OIE in post-surgical patients

Materials and Methods: A double-blind, randomised, parallel-group study compared single iv doses of ondansetron (ond) 8 mg, 16 mg and metoclopramide (met) 10 mg in the treatment of OIE in patients receiving parenteral opioid analgesia post-surgically. Emesis related to surgery itself was minimised by restricting patient entry to adult patients undergoing surgery types with low emetogenicity. Patients who required antiemetic within 6 h of receiving their first dose of post-surgical opioid were assessed for 24 h following study drug The proportions of patients who experienced complete control (ie no emetic episodes, no nausea, no rescue antiemetic medication and no withdrawal) at 24 h were compared (Mantel-Haenszel chi-squared test).

Results and Discussion: Of the 4511 patients enrolled, 1380 had OIE and received study medication. Preliminary results showed that ond 8 mg and ond 16 mg were significantly better than met 10 mg in controlling emesis and nausea ($p < 0.02$). There was no significant difference between the two ond groups ($p > 0.05$). The incidences of adverse events were low in all three treatment groups (14%–17%) (figure).

Conclusions: Preliminary data found that ond 8 mg and ond 16 mg iv were effective in the treatment of OIE following opioids administered post-surgically. No difference in efficacy was observed between the two ondansetron doses, but both were significantly better than met 10 mg

Acknowledgements: The authors thank the investigators who contributed to the study

A.459 Comparison of ondansetron and cyclizine in the treatment of early postoperative nausea and vomiting

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Background and Goal of Study: There is little published information on the treatment of postoperative nausea and vomiting (PONV) in the recovery ward, despite a suggested incidence of at least 10% [1] We compared the efficacy of ondansetron and cyclizine for the treatment of this problem

Methods: After Ethics Committee approval 250 patients of a mixed surgical cohort and experiencing nausea and/or vomiting in recovery were studied using a double-blind crossover design The severity of nausea and pain (4 point ordinal scales) and presence of vomiting were assessed by nursing staff. Patients were then allocated randomly to receive either iv ondansetron 4 mg (O) or iv cyclizine 50 mg (C) as initial treatment After 30 min symptoms were re-assessed and if further treatment was required escape (crossover) drug was given. Patients not responding to both drugs after a further 30 min were 'non-responders' Demographic (age, gender and weight), anaesthetic drug (pre-medication, induction, maintenance and analgesia), operation (type and duration) and recovery opioid data were also collected The primary outcome measure was the number of patients requiring escape treatment Chi-square and Student's t tests were used to analyse data $P < 0.05$ was considered statistically significant

Results: Incomplete data from 25 (O) and 24 (C) patients were rejected. Initial and 30 min nausea and pain scores, incidence of vomiting as well as demographic, anaesthetic and operation data were comparable between groups. 64% and 42% of patients in groups O and C respectively, received opioids in recovery ($P < 0.01$). The table shows the number of patients requiring escape treatment and non-responders

Group	Escape	Non-responders
O (n = 100)	24*	1
C (n = 101)	39	0

* $P = 0.026$

Conclusions: Although more patients in group O received opioids in recovery, this regimen was significantly more efficacious in the management of early PONV However, the use of ondansetron and cyclizine, in any order, is highly effective Economic evaluation suggests that although drug costs are higher using ondansetron as initial therapy, this may be offset by the smaller number of patients requiring escape treatment with benefits for the use of nursing time.

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A.460 Systemic *vs* single ondansetron administration in preventing nausea and vomiting as well as pruritus after intrathecal morphine administration

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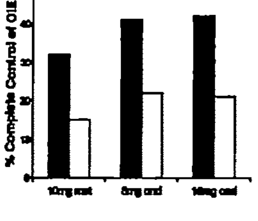
Background: The intrathecal administration of opioids is a simple and reliable method of providing long-acting postoperative pain relief. However postoperative nausea and vomiting (PONV) as well as pruritus seem to be important and frequent side-effects. It seems that ondansetron is effective in the prophylaxis of PONV. In addition it is postulated that ondansetron is a promising agent in the prevention of pruritus (1). In a double-blind randomized study we compared the efficacy of different regimens of ondansetron with placebo, in the prevention of PONV as well as pruritus following orthopaedic surgery, when using intrathecal morphine for postoperative pain relief.

Materials and Methods: In the study were included 65 patients, ASA I–III, aged 35–75 years and were given subarachnoid injection of plain



bupivacaine 0.5% mixed with morphine 0 3 mg for surgical and postoperative analgesia. Patients were randomly allocated in 3 groups. In group 1 (n = 21) they received i v. 2 ml of saline 20 min before the spinal, as well as at 12, 24, 36, 48 hours after surgery In group 2 (n = 24) patients received i.v ondansetron 4 mg 20 min before the spinal and i.v. saline 2 ml at 12, 24, 36, 48 hours after surgery. In group 3 (n = 20) ondnsetron 4 mg was given i v. 20 min before the spinal and at 12, 24, 36, 48 hours after surgery. In the postoperative period nausea scores, vomiting as well as pruritus scores and pain relief were recorded every 4 h interval over a period of 48 h

Results: Postoperative pain relief was excellent in all groups. Our results are summarized in the table.

Group	1	2	3
Nausea	12/21 (57.1%)	6/24 (25 0%)	5/20 (25%)
Vomiting	11/21 (52.4%)	5/24 (20 8%)	4/20 (20.0%)
Pruritus	15/21 (71 4%)	15/24 (62 5%)	9/20 (45 0%)

Fisher's exact test Nausea 1 vs 2 p = 0 03, 1 vs 3 p = 0 04, 2 vs 3 NS, Vomiting 1 vs 2 p = 0 03, 1 vs 3 p = 0 03, 2 vs 3 NS, Pruritus 1 vs 2 NS, 1 vs 3 p = 0 08, 2 vs 3 NS

Conclusion: Systemic i.v. administration of ondansetron is effective in the prevention of PONV after intrathecal morphine administration, but seems to offer no advantage over the single ondansetron administration. However the systemic i.v. ondansetron administration seems to be more effective in the prevention of pruritus

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A.461 Influence of intrathecal combination of clonidine with morphine on nausea and vomiting as well as pruritus

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Background: The intrathecal administration of opioids is a simple and reliable method of providing long-acting postoperative analgesia. The addition of clonidine to intrathecal bupivacaine increases both the duration of motor and sensory block as well as the duration of postoperative analgesia (1). It has been stated the theoretical hypothesis that the combination of alpha-2 agonists with opioids provides very durable analgesia with fewer side-effects than if either were used alone (2) In a double-blind randomized study we compared the efficacy of intrathecal clonidine in preventing postoperative nausea and vomiting (PONV) as well as pruritus, following major orthopaedic surgery, when using intrathecal morphine for postoperative pain relief

Materials and Methods: In the study were included 46 patients ASA I-III, aged 40–75 years well matched for characteristics and were given a subarachnoid injection of plain bupivacaine 0.5% mixed with preservative-free morphine 0.3 mg alone (group 1, n = 21) or with the addition of clonidine 1 μg/kg (group 2, n = 25) In the postoperative period nausea scores, vomiting as well as pruritus scores and pain relief were recorded every 4 h over a period of 48 h.

Results: Postoperative pain relief was excellent in both groups. Our results are summarized in the table·

Group	1	2	P-value*
Nausea	12/21 (57 1%)	4/25 (16 0%)	0 005
Vomiting	11/21 (52 4%)	3/25 (12 0%)	0 004
Pruritus	15/21 (71 4%)	8/25 (32 0%)	0 02

*Fisher's exact test

Conclusion: Our findings confirmed experimentally that the intrathecal combination of clonidine with morphine is very efficient in preventing PONV as well as pruritus

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A.462 Clonidine premedication in middle ear microsurgery

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Background and Goal of Study: Clonidine premedication has been used for isoflurane-induced hypotension during middle ear microsurgery to provide a relatively bloodless field (1–3) The purpose of this study was to determine if a single-dose oral clonidine premedication would 1) reduce the requirement of isoflurane and urapidil to get the desired hypotension and 2) decrease bleeding in patients undergoing middle ear surgery

Material and Methods: The study was approved by the local ethics committee, and informed consent was obtained from all patients Thirty one patients were designed randomly in two groups 14 received 0 3 mg clonidine p.o 1.5 h before surgery. The other 17 received placebo and served as a control group. The standardized general anaesthesia included propofol, isoflurane, N2O, fentanyl and atracurium. Bleeding was evaluated in four categories: from 0 (no bleeding) to 3 (severe) Data was analyzed throughout ANOVA.

Results: Mean age of patients was 38 2 yr ± 11 3 (clonidine) and 42 4 yr ± 13 2 (placebo), 11 male and 20 female, ASA I-III. The isoflurane concentration administered was lower in the clonidine group (0 64 ± 0 1 clonidine vs 0.96 ± 0 2 placebo, p < 0 001) The dosages of supplementary urapidil showed no differences between groups The quality of the surgical field was better in the clonidine group (1 1 ± 0 4 clonidine vs 0 74 ± 0 3 placebo; p < 0 05) Arterial blood pressure and heart rate were significantly lower in the clonidine group at intubation and postintubation No statistical differences were found in adverse effects between groups.

Conclusions: Clonidine premedication before anaesthesia was helpful in decreasing consumption isoflurane-induced hypotension and bleeding during ear surgery

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A.463 Effect of clonidine premedication on the induction dose of propofol and haemodynamic parameters

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Introduction: Clonidine is an alpha$_2$ agonist representing a new class of drugs being increasingly used in anaesthetic practice[1] Clonidine is known to have sympatholytic, anxiolytic, analgesic, anaesthetic-sparing and intra-operative haemodynamic-stabilizing effects[1]. Very little information is available on the effect of clonidine on the induction dose of propofol[2]

Aim: To determine the induction dose of propofol after oral clonidine premedication or placebo and to study the consequent haemodynamic effects, in a prospective, randomized, double blind study.

Methods: After ethical committee approval, 60 ASA I/II patients scheduled to undergo minor day procedure surgeries were randomly allocated to receive either clonidine 300 mcg (Gr1) or placebo (Gr2) as oral premedication 90 mins prior to the surgery Propofol was administered at the rate of 10 mg every 5 seconds till loss of verbal contact with patient Heart Rate (HR) and blood pressure (BP) were measured before (baseline), just after and 1, 3, 5 minutes after administration of sleep dose Recovery time was noted from turning off isoflurane to the patient stating their name Results were analysed with students t test and ANOVA

Results: Both groups were demographically matched for all variables The induction dose of propofol was significantly lower in the clonidine group than in placebo The recovery times were not significantly different Table shows mean ± S.D.

	Clonidine	Placebo	Significance
Induction Dose. mg/kg	1 74 (± 0 44)	2 08 (± 0 57)	P < 0 05
Recovery Time (mins)	9 84 (± 3 56)	8 44 (± 3 72)	None

The heart rate was significantly lower in the clonidine group compared to the placebo group at all intervals studied, as were the blood pressures (P < 0.01). Using ANOVA, the HR in the clonidine group did not change from the baseline, whereas in the placebo group it increased significantly at the 5 minute interval (P < 0.001). The blood pressure in the clonidine group was lower at all intervals compared to the base line (P < 0 001) Whereas in the placebo group, only the systolic BP was lower at all intervals compared to base line (P < 0.001)

Conclusion: This study shows that oral clonidine premedication reduces induction dose of propofol and decreases the heart rate and blood pressure when compared to the placebo The recovery times are similar in both groups

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A.464 Emergence and recovery from desflurane or isoflurane prolonged anaesthesia for acoustic neuroma surgical procedures

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Background and Goal of Study: The occurrence of a cerebellopontine angle hematoma is the major post-operative risk after acoustic neurinoma surgery by translabyrinthic approach. Therefore the necessary neurological post-operative assessment would benefit from a clear and rapid recovery. Desflurane (D) with its fastest kinetic profile among halogenated agents[1] could be a suitable alternative to the commonly used isoflurane (I) in this long-lasting surgery requiring also a smooth, deep and stable anaesthesia[2].

Materials and Methods: After institutional approval and informed consent, 30 patients selected for this surgery were randomized to receive either D or I in 50: 50 N_2O-O_2 mixture (1 L fresh gas flow) to maintain anaesthesia. Analgesia consisted in sufentanil continuous infusion (0.15 to 0 30 μg/kg). Times from end of anaesthesia to spontaneous breathing (SB), extubation, eyes opening, hand squeezing to command, ability to state name, birthdate and phone number were recorded together. The Steward recovery score was recorded also every 5 minutes during the 20 first post-operative minutes and then every 10 or 15 minutes. Statistics: Student T test bilateral, Wilcoxon rank sum test bilateral, Fisher exact test bilateral

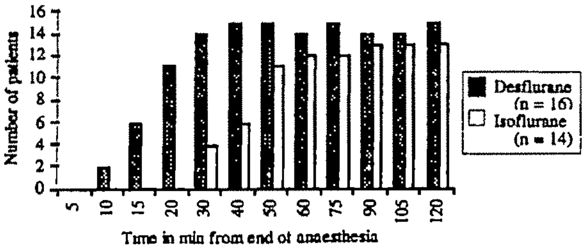

Fig. 1 Patients with Steward score to 6

Results and Discussion: The groups were similar regarding patients characteristics, depth of anaesthesia, sufentanil total dose, anaesthesia duration (D: 348.1 ± 18.9; I: 348.9 ± 22 8 min), hemodynamic/respiratory parameters and surgical conditions assessed by bleeding score. The emergence time was significantly more rapid in the D group and the orientation (ability to answer to name, birthdate and phone number) was fully recovered earlier in the D group. Steward scores were also better during the first post-operative hour in D group.

Times to recover (in min) after D vs I anaesthesia

	SB	Extubation	Eyes opening	Hand squeezing	Name	Birthdate	Phone number
D	9 7 ± 1 2	14 1 ± 2.4	14.9 ± 2.4	19.6 ± 3.0	22.1 ± 3.1	22.4 ± 3.1	24.3 ± 3.6
I	17 1 ± 1.4	26 1 ± 2 4	30 6 ± 2 7	34 2 ± 3.8	39 1 ± 4 6	46 5 ± 10 2	50 4 ± 10 3
p	≤0 001	0 001	0 001	0 005	0 006	0 039	0 029

Conclusion: Anaesthesia maintenance with D leads to similar preoperative conditions but allows a more rapid and clearer recovery in comparison with I. This recovery is particularly suitable after long-lasting surgical procedures justifying the full patients cooperation to make an early diagnosis of any neurological alteration.

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A.465 Effects of nitrous oxide as second gas during desflurane anaesthesia

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Background & Goal of Study: We have studied how N_2O influences desflurane uptake velocity in a heterogeneous population of adult patients.

Material & Methods: 50 patients scheduled for abdominal surgery under general anesthesia were randomly distributed in two groups: DNO (Desflurane – N_2O 60% – O_2 40%) and DAO (Desflurane – Air – O_2 40%) Desflurane was administered in both groups at 1.3 MAC-awake dose with an Ohmeda TEC-6 vaporizator (open circuit) with a fresh gas flow of 100 ml/kg. Desflurane uptake at 1, 5, 10, 15, 30 and 60 minutes was measured as the value of the Fet/Fi ratio (1, 2).

Results & Discussion: Desflurane uptake was higher in the DNO group in respect to DAO group at 5, 10, 15, 30 and 60 minutes. (Table 1)

Table I Percent uptake of desflurane in respect to the inspired concentration

	FET/FI (%)					
	1 m	5 m	10 m	15 m	30 m	60 m
DNO	68 6 (17.1)	88 0 (7 4*)	93 6 (5 1*)	94.6 (4 1*)	95 2 (3 8*)	95 8 (3 2*)
DOA	62.8 (9 5)	80 7 (3 5)	85 0 (3 8)	87 6 (3 8)	89 6 (2 9)	90 9 (3 3)

(*) p < 0 05

Conclusions: N_2O increases desflurane uptake velocity due the second gas effect. In order to achieve similar uptake rates without N_2O it is necessary to increase proportionally the desflurane Fi.

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A.466 Recovery profile of desflurane, propofol and isoflurane anaesthesia in morbidly obese patients: preliminary results

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Background & Goal of Study: Obesity is associated with physiologic changes that may alter drug disposition Fast recovery from anaesthesia is desirable so that airway patency can be reestablished and so that the patient can collaborate in chest physiotherapy. We compare the recovery time from desflurane (DES), propofol (PRO) and isoflurane (ISO) anaesthesia in morbidly obese patients undergoing bariatric surgery.

Material & Methods: After institutional approval and informed consent, 17 morbidly obese patients (14 females) with body mass index (BMI) as greater than 40 $kg.m^{-2}$ were enrolled in the study. Anaesthesia was induced with fentanyl 2 $\mu g.kg^{-1}$ and propofol 1.5 $mg.kg^{-1}$; succinylcholine was used to facilitate tracheal intubation. Anaesthesia was maintained with either DES, PRO or ISO in O_2: N_2O 50% and continuous infusion of atracurium. Fentanyl 1 $\mu g.kg^{-1}$ was injected every 30 min, or depending on patient requirements. End-tidal CO_2 pressure was recorded continuously to adjust minute ventilation Times to eye opening, to extubation, to verbal command and orientation to name and date of birth were recorded Statistical analysis was performed with one way analysis and significance considered at $p < 0.05$.

Results: The study groups were demographically similar Values are expressed as means (SD).

	DES (n = 5)	PRO (n = 6)	ISO (n = 6)
Age (y)	34 6 (8)	47.6 (7)	40 5 (11)
Weight (cms)	149 (38)	145 (37)	139 (26)
BMI (kg m^{-2})	59 (14)	53 (11)	51 (7)
Eye open (min)	7 2 (2 7)	5 6 (2 1)*	12 9 (4 4)
Extubation (min)	15.5 (8 7)	10 5 (6)	14 8 (5 2)
Orientation (min)	16 5 (8 6)	11 2 (6 2)	16 9 (5.1)

*P < 0 05 from DES and ISO.

Conclusions: In spite of a tendency for shorter times in the propofol group, only time to eye opening was significantly shorter. Duration of anaesthesia and opiates and muscle relaxant requirements were similar in all groups. In view of these preliminary results the study should be extended, enrolling a larger number of morbidly obese patients

Supported by Fondo de Investigaciones Sanitarias (FIS 94/617), Spain

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A.467 Isoflurane enantiomers in humans

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The isoflurane molecule has an asymmetric C- atom, the routinely used isoflurane is a racemate of (+)- and (−)-enantiomers. It is metabolized to 0.2% (1). However, animal and in vitro data suggest, that there are differences between the 2 enantiomers with respect to both, anesthetic potency and metabolism (2) Since the separation of the enantiomers is very challenging there are no data about the concentrations of isoflurane enantiomers in humans. In this study we measured the amount of isoflurane enantiomers in the blood of patients undergoing general anesthesia maintained with isoflurane racemate. The amount of the enantiomers were quantified at the end of anesthesia and every day for a period of 8 days after the operation. The study was proven by the Ethik Kommission of the Eberhard Karls university Tubingen

Material and Methods: Enantiomers of Isoflurane were determined using GasChromatography Mass Spectometry (GCMS). For the separation of the recemate a capillary column with a modified cyclodextrinphase was used 41 (25 female, 16 male) patients were included in the study (60 ± 14 yr-old; mean ± SD) after informed consent was obtained. They underwent different operative procedures. The duration of the surgeries was 194 min ± 97. The patients were ventilated via a nonrebreathing circuit Normalventilation was confirmed by capnometry. During surgery, balanced anesthesia was performed with 0.8 ± 0.2 Vol% Blood samples were drawn immediately after the extubation (day 0) and on days 1–8 in 24 patients. 8 patients denied further blood drawing after 5 days ($n = 6$) or 6 days ($n = 2$)

Results: Before the study get started, it was confirmed, that the applied Isoflurane racemate consists of exactly 50%(+) and 50%(−) enantiomers The coefficient of variation (CV) for the different concentrations observed were between 0.06 and 0.2%. The results express the area under the curve of the S(+) racemate [%]. In ASAI–II patients the concentrations of the S(+) enantiomer were between 51–52%. The highest concentration of the S(+) enantiomer was at day 2 In patients with liver diseases ($n = 6$) the S(+)-concentration was also elevated at day 2 (51.66 ± 0.46%, +0.97% in comparison to day 0) In adipose patients the S(+) concentration during the 8 days was +0.355% higher than in normal weight patients The applied Isoflurane concentration had no influence on the enantiomer concentration Also the duration of the operative procedure did not influence the enantiomer distribution.

Conclusion: Our data show that the ratio of 50% S(+) and 50% R(−) enantiomers in the applicated isoflurane racemate is changed in favor to the S(+) enantiomer in man By an overall metabolism of 0.2% a complete exclusion of one enantiomer from being metabolized would only lead to an enrichment of this enantiomer by 0.1%. These data could be explained by different metabolism of the S(+)- and R(−) enantiomers

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A.468 Reduction of minimum alveolar concentration of isoflurane by tramadol in comparison with morphine in rats

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Background and Goal of Study: Tramadol is a potent analgesic drug with combined opioid (μ effect) and nonopioid (inhibition of NE and 5-HT re-uptake) mechanism of action. The analgesic effect of tramadol is partially antagonised by naloxone, and fully antagonised only by the combination of naloxone and yohimbine ($\alpha 2$ adrenoceptor antagonist) (1). Clinical experience indicates that the administration of tramadol during anesthesia may result in prolonged awakening times. We questioned 1) whether tramadol has the potential to reduce the requirements for anesthetic drugs and 2) which mechanism of action predominates to produce this side effect.

Materials and Methods: Male Whistar rats (250–300 g) were chronically instrumented with a catheter in the internal jugular vein and in the carotid artery. Two days later the study was initiated· Rats were anesthetised with isoflurane, intubated and mechanically ventilated with 100% O_2 Ventilation was adjusted to obtain normal blood gas values. MAC determinations were performed using a standard technique (2), in 9 groups ($n = 10$ for each group). MAC was determined in the following conditions **A)** saline control, **B)** tramadol 10 mg/kg iv, and **C)** morphine 1 mg/kg iv. In addition in all groups the effect of antagonists was studied using: **1)** naloxone 5 μg/kg/min iv and **2)** yohimbine 1 mg/kg iv Data were analysed using two way anova followed by t-test when appropriate ($p < 0.05$)

Results and Discussion:

MAC of isoflurane in rats (mean ± sd)

	Control	Naloxone	Yohimbine
Saline control	1.38 ± 0.16	1.39 ± 0.19	1.37 ± 0.11
Tramadol	1.22 ± 0.18*	1.47 ± 0.13	1.16 ± 0.23*
Morphine	1.17 ± 0.19*	1.38 ± 0.23	1.14 ± 0.06*

* = $p < 0.05$ compared with saline control

Tramadol and morphine both reduce the mac of isoflurane to the same extent Addition of naloxone, but not yohimbine, antagonises this mac reduction

Conclusion: Reduction of anesthetic requirements by tramadol is comparable to morphine both in magnitude and mechanism of action.

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A.469 The analgesic potency of xenon and nitrous oxide in humans evaluated by experimental pain

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Background and Goal: The aim of the present study was to compare the analgesic potency of MAC-equivalent concentrations of Xenon (Xe 10, 20, 30 and 40 vol%) and nitrous oxide (N_2O 15, 30, 45 and 60 vol%) in humans using a multi-modal experimental pain testing and assessment technique

Methods: 12 healthy volunteers were tested in a randomised, single blind, cross-over study The following experimental pain tests were used the nociceptive reflex to repeated stimuli, pain tolerance to ischaemia, electrical stimulation, mechanical pressure, and cold The reaction time was also measured Due to nausea and vomiting results for all pain tests could only be evaluated for the two lowest concentrations (Xe 10 and 20 vol%, N_2O 15 and 30 vol%) At 30 vol% Xe and 45 vol% N_2O only results from the nociceptive reflex could be evaluated

Results and Discussion: Xenon and nitrous oxide both increased the threshold for the nociceptive reflex to repeated stimulations, the increased was higher for 30 vol% Xe compared to 45 vol% N_2O – Xe 10 and 20 vol% and N_2O 15 and 30 vol% increased the pain tolerance to ischaemia, and electrical stimulation. The increase in pain tolerance was higher for Xe compared to N_2O at both concentrations for ischaemia and at 20 vol% Xe compared to 30 vol% N_2O for electrical stimulation Xe 10 and 20 vol% and N_2O 15 and 30 vol% slightly increased the pain tolerance to mechanical pressure There was no difference in the increase caused by Xe and N_2O Xe 10 and 20 vol% and N_2O 15 and 30 vol% did not change the reaction to cold, although a slight increase in immersion time (time until hand was withdrawn) was recorded Xe 20 vol% and N_2O 30 vol% increased the reaction time, Xe more than N_2O Of 11 volunteers that could be tested with both Xe and N_2O nausea and/or vomiting was experienced by 9 with Xe and by 6 with N_2O.

Conclusions: The present study shows that xenon and nitrous oxide do not differ in their analgesic profiles Both attenuated pain induced with different modalities in a similar manner Xenon showed an analgesic potency that was at least 1.5 times higher than that of nitrous oxide Both evoked nausea and vomiting in a large number of volunteers.

A.470 Effective concentration$_{50}$ for propofol with 70% xenon *vs* 70% nitrous oxide

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Background and Goal of Study: Xenon has been reported to be a potent and safe anaesthetic [1] and thus supposed to be an alternative to nitrous oxide. We have determined the influence of 70% xenon on the reduction of the effective concentration 50 (EC50) for propofol compared to 70% nitrous oxide

Material and Methods: After obtained institutional ethic's committee approval and written informed consent, 60 female patients undergoing breast surgery were studied They were allocated randomly to receive either 70% xenon (PROP/XE) or 70% nitrous oxide (PROP/N2O) in oxygen. Anaesthesia was induced with propofol with an initial target plasma concentration of 4.5 $\mu g\ ml^{-1}$ using target controlled infusion (TCI) We applied a sequential study design If patients responded to skin incision, the next patient in that group received a target which was 0.1 $\mu g\ ml^{-1}$ higher and if the patient did not respond, 0.1 $\mu g\ ml^{-1}$ lower Response was defined as purposeful movements within 30 seconds after incision. EC50 values were calculated by probit analysis

Results and Discussion: The predicted EC50 for PROP/XE and PROP/N2O was 1.9 $\mu g\ ml^{-1}$ and 3.6 $\mu g\ ml^{-1}$, respectively Thus, the reduction of the predicted EC50 for propofol by xenon was 43% (figure).

Conclusion: We conclude that xenon appears to be 43% more potent compared to nitrous oxide

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A.471 Quantification of the electroencephalographic effects of propofol using semilinear canonical correlation

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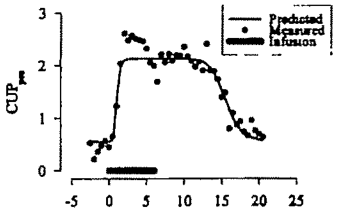
Background and Goal of the Study: The EEG is a powerful tool for the measurement of the central effects of hypnotic drugs A new statistical technique, semilinear canonical correlation (SCC), has been used in the analysis of EEG[1]. SCC extracts from the EEG a parameter maximally correlated with biophase concentration of the drug. The goal of this study was to obtain a descriptor of the effects of propofol on the EEG using SCC.

Materials and Methods: We analyzed EEG previously collected under IRB approval from 24 individuals who received propofol at a rate of 0.5 μg/kg/min until 3 seconds of burst suppression appeared in the raw EEG. The result of the EEG processing was a frequency spectrum every 20 sec containing powers in the 10 bins 0.5 Hz to 3 Hz, 3.5 Hz to 6 Hz, ..., 27.5 Hz to 30 Hz. The coefficients γ_1, ..., γ_{10} define an EEG effect measure $E = \Sigma^{10}{}_{i=1}\gamma_i E_i$, herein called the propofol canonical univariate parameter (CUP_{pro}), where Ei is the natural log of the power in the ith frequency bin. The details of the analysis are described in Gregg et al.[1] Using SCC we estimated these ten coefficients in a "learning sample" of 16 individuals. Then the median of these coefficients, were validated in the remaining 8 individuals in whom we also estimated the pharmacodynamic (PD) parameters k_{e0}, IC_{50} and slope of the curve, according to a sigmoid E_{max} model.



Results and Discussion: The graph shows the time course of effect CUP_{pro} in the worst individual according to R^2 criteria (R^2. = 0 77) The median (range) PD parameters were k_{e0}: 0.18 (0 1–0 3), IC_{50}' 1 68 (1 26–2 5), slope: 4.67 (3.4–15.8). R^2. 0 86 (0.77–0.94).

Conclusion: The CUP_{pro} that we obtained is a sensitive measure of the hypnotic effects of propofol reflected in the EEG. Further research is needed to investigate possible effect of covariates on the PD of propofol.

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A.472 Assessment of drug-drug interactions in patients receiving postoperative analgesia by intravenous PCA

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Background & Goal of Study: In the treatment of pain, drug combinations are used to produce effective analgesia while decreasing side effects. The drugs can have an independent action (no interaction) or show synergy or antagonism. The evaluation of an interaction requires pre-designed experiments, sometimes difficult to perform in humans. Our aim was to validate an alternative method to assess drug interactions, using intravenous PCA.

Material & Methods: 101 patients undergoing abdominal histerectomy entered the study Institutional and individual consents were obtained Patients were distributed into groups that received at the time of analgesia request (TAR) one of the following treatments by i v. PCA (randomized, double blind)

Group	Tramadol·Metamizol		Patient Number
	Ratio	Dose	
1	1 0	10 0	21
2	0·1	0 120	21
3	1 1	5 60	20
4	1 0 3	7 5 30	19
5	1 3	2 5.90	20

Tramadol (TR) and Metamizol (MTZ) were administered at fixed ratios based on a relative analgesic potency of 1:12. PCA parameters were: loading dose 10 ml, 2 ml boluses, lockout interval 15 min, maximal dose 50 ml/24 hrs Pain intensity (VAS), number of boluses requested/delivered, and side effects were assessed at TAR and 15 min, 1, 2, 4, 8, 12, 20 and 24 hrs afterwards. Isobolograms, one-way ANOVA, t and χ^2 test were used for statistical evaluation.

Results & Discussion: Groups were comparable regarding demographic data, duration of surgery and TAR. No significant differences between groups at any time point were observed regarding· VAS, % relief, efficacy of the treatment (expressed as the number of patients/group experiencing a $\geq$ 50% pain relief), n° of boluses, or side effects; these results demonstrate that all treatment groups were comparable. The isobolographic analysis of the doses required to produce the same analgesic effect, showed a significant ($P < 0.05$) synergistic interaction between TR and MTZ when combined in a 1.1 ratio (group 3) at the following time points: 8, 12, 20 and 24 hrs No interaction could be demonstrated with the other combinations.

Conclusions: Our study shows that the evaluation of drug interactions can be documented using fixed ratios of the drugs of study, administered by intravenous PCA when a coinciding analgesic end point is achieved.

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PAEDIATRIC ANAESTHESIA AND INTENSIVE CARE

A.473 Which method of induction with sevoflurane in children. Incremental or high concentration, with or without nitrous oxide?

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Introduction: Induction of anaesthesia is usually performed with incremental concentrations of volatile agent in an O2/N2O mixture in order to reduce the concentration of volatile agent and to speed the induction. Sevoflurane (S) is a non pungent volatile agent and therefore could be administered in O2 alone and with initially high concentration. This study was designed to evaluate these methods of induction

Methods: 65 children aged 20–137 months, ASA I–II, scheduled for tonsillectomy, were prospectively and consecutively allocated to 3 groups (gr) according to the method of induction Premedication was performed 20 min before induction with 0 3 mg/kg rectal midazolam. Gr HC-O2 inhaled 7% of S in O2, gr IC-O2 inhaled incremental concentrations of S in O2 (2%, 4%, 6%, 7% every 5 breaths) and gr HC-N2O inhaled 7% of S in an O2-N2O mixture (50%-50%). Oro-tracheal intubation was performed after insertion of an IV canula, without the use of myorelaxants or opioids Characteristics of induction were recorded by an independent observer and hemodynamic measurements were recorded every minute (Datex). Results are expressed as mean ± SD. Statistical analysis used ANOVA or Chi-square test when appropriate

Results: Demographic data were identical in the 3 gr Loss of eyelash reflex and central miosis occurred sooner in gr HC-N2O than in the 2 other groups, but tracheal intubation was performed at the same time An oropharyngeal canula was inserted before 2 minutes in those patients with obstructive airway No complication such as laryngospasm was observed An increase in SAP and HR was observed between the 2nd and the 4th minute of induction in the 3 groups with no difference between groups

	HC-O2	IC-O2	HC-N2O	
n	23	22	20	
Age (months)	58 ± 28	53 ± 18	60 ± 24	ns
Weight (kg)	18 ± 6	18 ± 5	18 ± 6	ns
Obstructive airway %	65%	77%	75%	ns
Duration anaesth (min)	54 ± 9	52 ± 11	55 ± 13	ns
Good mask acceptance %	87	95 5	100	ns
Poor mask acceptance%	13	4 5	100	ns
Oropharyng canula (sec)	114 ± 41	113 ± 26	100 ± 14	ns
Eyelash reflex (sec)	61 ± 12	85 ± 16	46 ± 9	p < 0 001
Central miosis (sec)	243 ± 56	287 ± 44	230 ± 43	p < 0 05
Tracheal intubation (sec)	320 ± 69	337 ± 59	292 ± 52	ns
Coughing %	13	9	0	ns
Apnoea %	0	0	10	ns
Agitation %	57	27	25	p = 0.053
Arrhythmia %	4	0	5	ns
FE sevo before TI (%)	5.5 ± 0 5	5.6 ± 0.6	5 6 ± 0.6	ns
SAP initial (mmHg)	107 ± 15	108 ± 12	109 ± 11	ns
ΔSAP (%)	19 ± 13	13 ± 14	14 ± 15	ns
HR initial (bpm)	106 ± 25	103 ± 24	101 ± 19	ns
ΔHR (%)	44 ± 30	40 ± 18	43 ± 28	ns

Conclusion: This study demonstrated that the 3 methods of induction could be used with no severe adverse event, even if the incidence of agitation during induction seems to be more frequent when sevoflurane is administered at high concentration in O2 alone. The addition af N2O allows for more rapid induction with less adverse effects.

A.474 Quality of recovery in children: sevoflurane *vs* propofol

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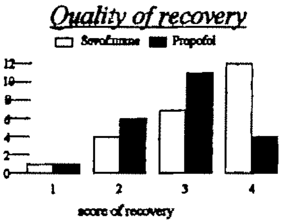
Background: Sevoflurane is a volatile anaesthetic permitting rapid recovery. Propofol-anaesthesia is recognised for it's rapid and clear-headed emergence. This study was designed to compare the emergence and recovery characteristics of sevoflurane and propofol anaesthesia in children scheduled for elective tonsillectomy.

Material and Method: Fifty children aged 3–10, ASA I/II, were randomly assigned in two groups Group P anaesthesia was induced with propofol 3 mg/kg iv and maintained with a propofol infusion 100–250 μg/kg/min. Group S: anaesthesia was induced with 7 vol.% sevoflurane and maintained with 2–3 vol.% sevoflurane. After intubation, ventilation was controlled to maintain normocapnia and all patients received N2O/O2 60/40 vol % for induction and maintenance of anaesthesia. At the end of surgery, infiltration of operative site was done with bupivacaine 0.25 mg/kg for postoperative analgesia The following parameters of emergence were recorded (1) delay from the end of anaesthesia (EA) to extubation, (2) time between the EA and first adequate response to simple command, (3) time spent in the recovery room Five minutes after the arrival in the recovery room, a sedation score was performed as follows **1:** sleepy and barely rousable, **2:** sleepy and easily rousable, **3:** awake and calm **4:** awake and agitated The incidence of nausea, vomiting and excitement was also studied All time data were compared with Mann-Whitney test The incidence of unwanted side-effects was analysed by the Fisher test. A $p < 0.05$ was considered significant

Results and Discussion:

Parameters of emergence

	Sevoflurane	Propofol
(1) Time to extubation (min)	14 ± 3.4	14.7 ± 5.6
(2) Delay to command (min)	21 ± 6	21 ± 7
(3) Time to discharge (min)	45 ± 14	50 ± 15



The quality of recovery shows a predominance of score 4 in the sevoflurane group The incidence of post-operative excitement was significantly higher in the sevoflurane group (46%) than in the propofol group (9%) ($p = 0.008$). The incidence of nausea and vomiting was the same in both groups

Conclusion: Sevoflurane provides an emergence as fast as propofol but with a higher incidence of agitation

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A.475 May sevoflurane be preferred to halothane in paediatric ophthalmological anaesthesia?

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Background & Goal of Study: It has been suggested that sevoflurane may be a reasonable alternative to halothane in children with respect to hemodynamic stability in induction and emergence from anaesthesia (1). However, the effect of anaesthetics on intraocular pressure must also be taken into consideration for paediatric ophthalmologic anaesthesia There is only one non-comparative study reported that sevoflurane does not significantly change intraocular pressure in children (2). The goal of our study was to evaluate the effect of sevoflurane on Intraocular pressure in children comparing with that of halothane

Materials & Methods: A double blind and randomized study design was used to investigate Fourty ASA class I patients, aged between 1 and 12 years, who would have been planned elective surgery and with no ocular diseases, were divided into two equal groups Sevoflurane or halothane was used incremental doses for induction. Tracheal intubation was performed three minutes after intravenous administration of 0.15 milligrams kg-1 of vecuronium Measurements of intraocular pressure were made using the Perkins hand-held applanation tonometer, at the times of ocular fixation, immediately before and after tracheal intubation For statistical evaluation, ANOVA and t-tests were used. Data are expressed as mean ± standard deviation. $P < 0.05$ was considered significant.

Results & Discussion: Both groups were comparable for demographic data In sevoflurane group, the intraocular pressure values (mmHg) at the times of ocular fixation, immediately before and after tracheal intubation were 14.5 ± 4.1, 10.4 ± 4.6, and 14.1 ± 6.1 respectively, and in halothane group those were 13.2 ± 4.9, 10.6 ± 4.2, and 14.2 ± 5. There were no statistically significant differences between the two groups and within each group

Conclusion: We concluded that the effect of sevoflurane on intraocular pressure in children does not differ from that of halothane and may be used safely in paediatric ophthalmologic anaesthesia.

A.476 Neuromuscular effects of mivacurium in children. Effect of sevoflurane

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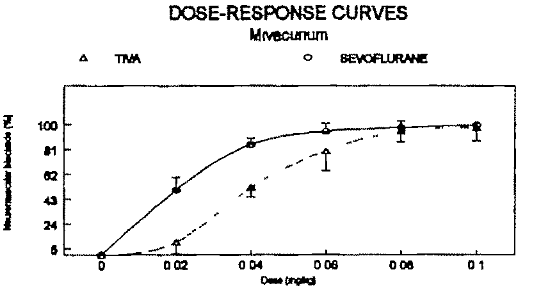
Background & Goal of Study: It is know that the potency of muscle relaxants are increased by volatile anesthetics The purpose of this study was to asses the potency of single dose mivacurium during anesthesia with sevoflurane and total intravenous anesthesia (TIVA)

Material & Methods: After approval by local ethics committee and written informed consent, the neuromuscular effects of mivacurium were evaluated in 60 children during sevoflurane and TIVA anesthesia for short procedures

Following inducción of anesthesia (propofol 2 mg/kg, fentanil 5 μgr/kg) the patients were randomly assignated to receive 1.5 MAC Sevoflurane or TIVA (propofol 8–12 mg/kg/h) and twenty minutes latter to receive one of the following doses of mivacurium (0.02, 0.04, 0.06, 0.08, 0.1 mg/kg) Neuromuscular response was evaluated by measuring the evoked twitch tension of the adductor pollicis muscle in response to supramaximal train of four (TOF) stimulation of the ulnar nerve at the wrist Peak twitch depression was determined following each bolus. The ED_{50} ED_{90} and ED_{95} neuromuscular blocking were calculated from logarithmic regresión análisis Two way analysis of variance was used for statistical análisis In all cases $p < 0.05$ was considered statistically significant

Results & Discussion: The dose response of mivacurium was significantly shifted to the left in sevoflurane group compared with TIVA group. (Fig.) ED_{50}, ED_{90} and ED_{95} were significantly lower in sevoflurane group (Table)

	TIVA	Sevoflurane
ED_{50}	0.040	0.013
ED_{90}	0.078	0.057
ED_{95}	0.085	0.068



Conclusion: Our data show that sevoflurane increase the potency of mivacurium in children undergo short surgical procedures Thus, we thing is necessary, to reduce the dosage

A.477 Endotracheal intubating conditions after cisatracurium in infants and children

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Background: Cisatracurium (Nimbex) is one of the ten stereoisomers which comprise atracurium but is not associated with dose-dependent histamine release in children and adults[1, 2] In this study we determined the intubation conditions and time course of action of cisatracurium in infants and children during N_2O-O_2-halothane or N_2O-O_2-opioid anaesthesia

Methods: With ethics committee approval and informed parental consent, 180 healthy paediatric surgical patients aged 1 month–12 years were studied. Premedication consisted of midazolam 0.2–0.3 mg/kg intranasally or 0.5–0.7 mg/kg orally. Patients were randomised for induction and maintenance of anaesthesia with either N_2O-O_2-halothane (Group H, n = 90) or with N_2O-O_2-thiopentone-fentanyl (Group O, n = 90) Following induction of anaesthesia, cisatracurium 0.15 mg/kg was administered by rapid (5 s) intravenous injection, intubation was started 120 s later and completed within 15 s Intubation conditions were scored using standard criteria: 1 = excellent, 2 = good, 3 = poor, 4 = impossible. Neuromuscular function was monitored using single twitch stimulation at 10 s intervals (Datex Relaxograph).

Results: See table 1 Satisfactory (excellent or good) intubating conditions were obtained in 98% of patients after cisatracurium 0.15 mg/kg; there was no significant difference between the groups Onset time was shorter and recovery time longer in patients anaesthetised with halothane than with opioid. There were no significant changes in heart rate or blood pressure.

Intubation conditions, onset and recovery times

Variable	Group H	Group O
n	90	90
Satis Intubation Conditions No. (%)	88 (98%)	85 (94%)
[95% CI]	[0 92–1 00]	[0 88–0 98]
n	89	89
Time to Max Block (min)	2 6*	3 0
Mean (SD)	(1 0)	(1 5)
n	84	88
Time to 25% Recoery (min)	46 2†	41 1
Mean (SD)	(8 4)	(9 0)

* $P < 0.05$, † $P < 0.001$ (Welch's t-test)

Conclusion: Cisatracurium is a promising non-depolarising neuromuscular blocking drug for use in infants and children. In common with other neuromuscular blocking agents its clinical effects are potentiated by halothane

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intubating conditions, infants, childrencisatracurium

A.478 An audit of simple dental extractions in children. Chair dental anaesthesia or the laryngeal mask?

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Background and Goal of Study: Fewer anaesthetists are willing to undertake chair dental anaesthesia (CDA)[1]. An alternative technique is the laryngeal mask airway (LMA) with patients in the supine position We have recently converted a CDA list into a LMA list. We compare these two techniques administered by consultant anaesthetists

Materials and Methods: We audited children undergoing simple dental extractions, 50 at the dental hospital using the LMA (group 1), and 50 in general dental practice using CDA (group 2). Induction was with propofol or N_2O, O_2 & sevoflurane. Co-operation at induction was assessed using the Frankl behaviour scale[2]. Ease of surgical access was graded 1–4 In group 1 we documented problems with the LMA. A fibreoptic assessment made of its position and tracheal blood soiling was noted.

Results and Discussion: 96% of group 1 had an iv induction and 74% of group 2 had an inhalational induction. There was no significant difference in the Frankl scale. Surgical access was significantly better in group 1 ($p < 0.05$). In group 1, two patients required intubation, one patient required jaw support throughout and fibreoptic assessment showed two patients with traces of blood in the trachea

Demographic details and times (mins secs)

	Group 1	Group 2
Age m (SD)	8 14 (3.2)	7.9 (2 8) *NS*
Sex M F	28·22	22 28 *NS*
No of Teeth m (SD)	7 24 (3 8)	3 5 (2 5)**
Time 1 m (SD)	163 (25)	40 (11)**
Time 2 m (SD)	5.45 (1 38)	2 16 (0 35)**
Time 3 m (SD)	4 27 (3.12)	1:5 (0 42)**
Time 4 m (SD)	6 23 (2:23)	4·43 (2 16)**
Time 5 m (SD)	62 19 (16·44)	16 10 (4·23)**

NS non significant, $^{*}p < 0.05$, $^{**}p < 0.01$, m (SD)-mean (standard deviation). Times. 1 = total time, 2 = induction to start surgery, 3 = operating, 4 = end surgery to hand over to recovery staff, 5 = start of anaesthesia to discharge home

Conclusion: The LMA technique is a suitable alternative to CDA, but takes longer. This may be because more teeth were extracted, indicating a change in referral practice, but may also reflect a different attitude to day case anaesthesia in the hospital compared to the community.

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A.479 Suitability of behavioural items for the assessment of postoperative pain in infants

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Introduction: The assessment of postoperative analgesic demand in infants is still a problem, since there is no observational system, which has been proven to be economic, valid, sensitive, specific and reliable. We therefore tried to find out prospectively, which of the proposed observational items fulfills these criteria (1–3).

Material and Methods: 13 observational items were included. crying, facial colour, facial expression, forehead's folding, nasolabial foldings, posture of arms, fingers, toes, trunc, legs, motoric restlessness, muscle tone, sweating and state of arousal. They were scaled according to their kind of expression in no, mild or high pronounciation corresponding to 0, 1 and 2 points. During the first postoperative hour all items were scaled in five-minute-intervals by one observer/infant (139 infants, 13 sets, 5 observers). A factor analysis was computed using the 13 different sets and the data of all sets together (principal components; Scree-test, Kaiser-Criterion). A substantial loading on the factor of less than |0 4| at any time excluded the concerned item. This procedure was repeated with the remaining items until any item had a substantial loading of at least |0.4| at any occasion Selectivity of the items were tested using the product-moment-correlation. Finally 5 items built a scoring system. Systemic sensivity and specifity of this set of items were calculated by discriminant analyses Constructive validity was tested using Piritramide ($N = 41$) and Ketamine ($N = 7$) Significance was accepted with $p < 0.05$

Results: Due to insufficient substantial loadings 3 items had to be eliminated. The factor analysis finally resulted in a one-factorial solution with 73% explained variance. The selectivity was highly significant with values between 0.74 and 0 90. For economic reasons 4 items with the least substantial loadings were eliminated (forehead's folding, posture of fingers, posture of toes, posture of arms) 5 remaining items (Crying, facial expression, posture of the trunc, posture of the legs, motoric restlessness) showed a high internal consistency ($\alpha = 0.927^{***}$) The score was reduced in any case using Piritramide or Ketamine. The discriminant analysis resulted in high values for sensitivity (87.9%), specifity (87.1%), positive predictive value (29 3%) and negative predictive value (99.2%).

Conclusion: we identified 5 observational items to be suitable for the assessment of postoperative pain in infants. They build a scoring system which was proven to be economic, sensitive, specific, reliable and valid. Its use in clinical practice and scientific research should be recommended

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A.480 Comparison of two paediatric pain scores in urological surgery

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Purpose: To compare to pain scoring system in the postoperative urologic surgery in paediatrics.

Material and Methods: Forty-five children (above 13 yr) undergoing urologic surgery were simultaneously assessed using two different pain scoring system The pain scoring systems used were the Objective Pain Score[1] (OPS) and Faces Rating Scale[2] (FRS).

Postoperative pain was evaluated by nurses trained in the paediatric postoperative patients at 0, 30, 60, 120, 180 minutes and every six hours.

Statistical analysis was performed using the χ^2 test and $p < 0.05$ was regarded as significant

Results: Forty-five ASA I patients were included in the study. Demographic data were. age 5.7 ± 3.6 (0.08–12 5 yr.), weight 23.3 ± 13.1 (3.7–59 Kg.), height 110 ± 32 (52–158 cm.). There was a high coincidence between OPS and FRS. The contingency coefficients for OPS and FRS in recovery were: 0.76 ($p < 0.0001$) at 0 minute, 0.79 ($p < 0.0001$) at 30 minutes, 0.66 ($p < 0.0001$) at 60 minutes, 0.81 ($p < 0.0001$) at 120 minutes, 0.76 ($p < 0.0001$) at 180 minutes, 0 63 ($p = 0.003$) at 9 hr., 0.70 ($p < 0.0001$) at 15 hr., and 0.61 ($p = 0.0011$) at 21 hr.

Conclusions: Facial Rating Scale appeared to be similar to Objective Pain Score in paediatric patients undergoing lower abdomen surgery. The FPS was easier to use than OPS and showed a realistic distribution of scores with respect to OPS.

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A.481 Clonidine prolongs bupivacaine spinal anaesthesia in newborns

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Spinal anesthesia (SA) allows sub umbilical surgery without general anesthesia in newborns, thus avoiding post anesthesia apnea. Plain bupivacaine (B), 1 mg/Kg, provides long enough block in only 50–70% of patients (1). Clonidine (C) prolongs sensitive and motor spinal block in adults (2). In infants, C has been successfully used to lengthen epidural block (3). Yet, C may have sedative effects which must be avoided in newborns. A prospective randomized study was designed to investigate duration, sedative and hemodynamic effects of C-supplemented SA in newborns.

Methods: Infants undergoing elective inguinal hernia repair were enrolled after institutional approval and parental consent. They were allocated to receive via the spinal route either 0 5% plain B: 1 mg/kg or B plus 0.25, 0.50 or 1.0 μg/kg C. The number of patients to be included was calculated from the available data on SA in newborn to reach 50% increase of SA duration and $\beta = 0\ 1$. Nine patients were required in each group Non invasive arterial pressure, heart rate and SpO2 were recorded before SA and every 3 minutes thereafter. Sensitive block extension was assessed by skin pinching at 2, 5 and 10 min. SA duration was defined as the time between injection and hip movement recovery. Sedation and ventilatory status were scanned carefully. Results are presented as median (25–75 percentile). Mann-Whitney-Wilcoxon test was used for comparison between groups. $p < 0.05$ was considered significant.

Results: At the time of surgery, the patients were aged 44 (40–45), 41.5 (39–43), 42 (39–46), 40.5 (37.6–42) weeks post conception, respectively. Anthropometric features, % of ex-premies, extention of SA, occurrence of respiratory problems or anesthetic supplementation were similar in all groups. Decrease in MAP was comparable in all groups: 18 (8–24); 22.5 (12–34); 30 (16–37) and 29 (19–38) % respectively (NS). Durations of the blocks are presented in the table

	B	B + C 0 25	B + C 0 5	B + C 1 0
N	11	18	13	10
Block (min)	67	85	93	103.5
25–75 percentile	(58–82)	(62–108)	(68–110)	(87–113)
p vs control	–	0 12	0 06	0 01

Conclusion: C increases significantly the duration of SA in newborns without deleterious side effects Despite a wide range of individual values, C provides a dose related increase in SA. Further investigation is needed to confirm these data.

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A.482 Effects of spinal anaesthesia with pethidine as sole agent, on plasma cortisol and glucose concentrations after lower abdominal surgery in children

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Background and Goal of Study: The spinal administration of local anaesthetics supress the neuro-endocrine response to surgery (1). In intrathecal administration pethidine has both opioid and local anaesthetic properties (2). We investigated the haemodynamic and stress hormone responses to surgery when spinal anaesthesia was performed with pethidine in comparison with bupivacaine.

Materials and Methods: With Ethical Committee and parents approval, 40 children 3–12 years old were divided into two equal groups, in a randomised, prospective study. According to the body weight $\leq$ 15 kg or $\geq$ 15 kg) the patients received 1.1 mg/kg and 1 mg/kg pethidine 5% (group P) or 0.4 mg/kg and 0 3 mg/kg (group B). A superficial halothane anaesthesia by facial mask in spontaneous ventilation was used for the maintenance of hypnosis. The onset time and duration of sensory block, the blood pressure and heart rate were recorded during the operation. Glucose and cortisol blood levels were measured 1 min before skin incision and at 4 h and 24 h after incision Results were analysed using two way ANOVA. Data were expressed as mean ± SD. $p < 0.05$ was considered significant.

Results and Discussion: No differences were identified between the two groups in terms of demographic variables and haemodynamics. The sensory block was satisfactory in both groups, with the onset faster in group P ($p < 0.001$). In comparison with preoperative values the cortisol levels significantly increased 4 h postoperatively in both groups ($p < 0\ 001$) Glucose levels decreased in both groups but significantly only in group B No significant differences were found between the two groups concerning cortisol and glucose blood levels.

Conclusions: In intrathecal administration pethidine developed a satisfactory sensory block with haemodynamic stability Although in comparison with preincision values, cortisol concentration increased, the hyperglicemic response was suppressed after both agents attesting the local anaesthetic properties of pethidine.

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A.483 Long-term epidural anaesthesia with ropivacaine in a small child

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Background: High plasma levels of bupivacaine occurred after continuous epidural infusion of more than 50 hours [1]. Ropivacaine is assumed to be less toxic compared to equipotent doses of bupivacaine [2]. We now report for the first time the use of ropivacaine for epidural long-term anaesthesia in a small child.

Method: A 21-months-old girl (11 kg body weight) was scheduled for brachytherapy of a vaginal rhabdomyosarcoma. Radiation was performed via a painful applicator filling the whole vaginal cavity After written parents' consent a continuous infusion of ropivacaine 0.5% was initiated at a rate of 2 5 ml h^{-1} (1 14 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$) via an epidural G 23 catheter (L4/5) with optional bolus (3 ml every 30 minutes) to achieve the required analgesia and partial immobilisation. After 51.5 h ropivacaine 0 75% was administered for a 26.5 h period at the same rate but with a 4 ml bolus option Sensory block, motor block, heart rate and peripheral oxygen saturation were monitored. Blood samples for the determination of the ropivacaine plasma level were taken after 22 and 70 hours.

Results and Discussion: During the entire treatment period (78 h) no respiratory, cardiovascular or toxic side effects occurred Satisfying anaesthesia including the intended partial motor block was only obtained by an increasing number of boli and augmentation of the concentration (3rd day). Nevertheless sensory block did never exceed the T8 level The average amount of ropivacaine rose from 1.4 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ (1st day) to 1.5 $mg{\cdot}kg^{-1}\ h^{-1}$ (2nd day) and 3 $mg\ kg^{-1}{\cdot}h^{-1}$ (3rd day) suggesting tachyphylaxis. Surprisingly the plasma levels (1 8 $\mu g{\cdot}ml^{-1}$ and 1 5 $\mu g{\cdot}ml^{-1}$ after 22 h respectively 70 h) even decreased.

Conclusion: Ropivacaine 0.5% and even 0.75% proved to be effective and safe during brachytherapy for continuous epidural long-term anaesthesia in a 21-months-old child over 78 hours. Surprisingly, the plasma level of ropivacaine decreased despite a more than two-fold increase in dosage during 70 hours Since plasma levels of 4 $\mu g{\cdot}ml^{-1}$ in adults are regarded as toxic threshold concentration, these data confirm the safety of ropivacaine even with increasing doses due to tachyphylaxis. In contrast, bupivacaine was reported to accumulate in adults [1]. Enzyme induction and increased metabolism might be an explanation in this child.

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A.484 Technical aspects of paediatric epidural catheter insertion: a prospective study of 338 cases

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Introduction: Since 1986, epidural analgesia is routinely used in our hospital to provide postoperative analgesia for children undergoing major surgery. This prospective study was undertaken to evaluate the incidence of technical problems encountered at the time of insertion of the EC.

Population & Methods: All EC inserted in children <15 years-old from Oct 1995 to Oct 1997 were included in the study. Demographic and technical data were collected on a special data sheet. Epidural analgesia was used only for major surgery and with oral consent of the parents. All EC were inserted under general anaesthesia A 18 or 19 G (if <12 kg) Tuohy needle was used to insert the EC using the median approach and the loss of resistance to "saline + a bubble of air technique" (1). The epidural space was punctured at the dermatomal level involved by surgery and the EC was threaded only of few cm into the epidural space. Chi-square was used to assess statistical significant

Results: A total of 338 EC were inserted· 176 and 162 EC were inserted through 18 and 19G needles, respectively. Their distribution according to level of puncture and body weight (bw) is shown in the table, as well as the number of cases in which the EC could be inserted at 1st attempt.

BW, kg	<5	5 1–10	10 1–20	20 1–30	>30
(n)	(23)	(88)	(120)	(74)	(33)
<T10	6	16	29	19	11
T10-L2	11	31	22	15	6
>L2	6	41	69	40	16
1st attempt	11	62	91	61	24
IES (%)	9 (39.1)	17 (19 3)	25 (2)	7 (9 4)	4 (12.1)
TEC (%)	4 (17 3)	11 (12 5)	4 (3 3)	2 (2 7)	3 (9)

As shown in the table, the most often reported technical difficulties were problems identifying the epidural space (IES) or threading the EC (TEC) Both were significantly (IES p = 0.018) (TEC p = 0.014) more frequent in children less than 10 kg No morbidity was associated with the insertion of these EC; only one dural tap occurred, in the 10.1–20 kg group

Conclusion: In our series, the incidence of technical complications at the time of EC insertion was low: 74% of EC were inserted at 1st attempt However, both identification of the epidural space and the insertion of the EC were more difficult in children <10 kg Our incidence of dural taps (0.3%) was much lower than reported by Dalens (1.8%) using similar needles but loss of resistance to saline or air (2).

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A.485 How reliable are oscillometric blood pressure monitors in neonates and infants?

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Background and Goal of Study: Non-invasive blood pressure measurements with automated oscillometric devices is considered to be safe and reliable. The objective of this study was to evaluate the performance of four blood pressure monitors, which are frequently used with neonates and infants.

Materials and Methods: A simulator[1] developed by the PTB, which allows the synchronized playback of real data records, was used for the assessment of the reproducibility and for the comparison of the oscillometric devices (SpaceLabs, Hewlett-Packard, S&W Medico and Critikon). The signals used for the simulation were obtained from 24 preterm and term neonates and infants, aged between 6 and 93 days and weighing between 902 g and 3500 g. 24 oscillometric signals were used for the simulation (one from each patient). Each signal was repeated 20 times for the systolic, diastolic and mean arterial pressure.

Results and Discussion: The reproducibility-coefficients were between 8 mmHg and 18 mmHg. Blood pressure fluctuations in (critically ill) neonates need to be observed accurately in the range of 5–10 mmHg (estimated range of autoregulation)[2], which is precluded by the performance of the oscillometric monitors. The test of agreement by Bland and Altman[3] generated 'limits of agreement' (consistent with ± 2 SD around the mean differences), which were invariably high for each monitor (average of 20 mmHg).

Conclusions: Single blood pressure measurements with the four oscillometric devices cannot be considered as reliable. These monitors, revealing a significant lack of (clinically satisfactory) agreement, should be regarded as different methods of blood pressure measurement, especially since the oscillometric method is not standardized and the algorithms employed to determine the blood pressure vary with the manufacturers and are not disclosed by them.

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A.486 An alternative method to determine the size of laryngeal mask airway in children

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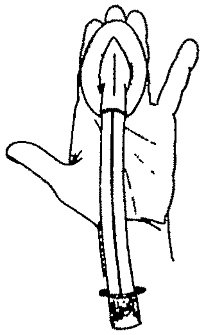
Background & Goal of Study: The size of laryngeal mask airway (LMA) in paediatric anaesthesia is usually determined according to the weight of the patient[1]. However, in some cases this parameter cannot be obtained. We propose a new method, easy and applicable at the bed-side. To validate this procedure, the sizes of LMA determined with this method are compared with the sizes according to the patient's weight

Materials & Methods: 117 paediatric patients, aged from one month to 14 years and without anatomical and/or nutritional disorders, entered the study. In every patient, the hand was opened separating the first and the 5th fingers, keeping the 2nd, 3rd and 4th fingers extended and together Different LMA sizes, inflated with the maximal standard volumes[1], were applied to the ventral side of the hand, keeping the widest part of the LMA on line with the widest part of the three fingers together The LMA best fitting these three fingers was chosen (figure). For every patient, this size was compared with the suggested size of the LMA considering the patient's weight. Kappa coefficient (κ) was used to evaluate the agreement between both methods.



Results & Discussion: The table shows the number of patients for every possible combination of MLA sizes, determined by patients' weight and by the fingers' method. Italic numbers indicate the patients (100 children, 85%) in which the size of the LMA coincided with both methods.

MLA Size		Size according to Weight				No patients
		1	2	2 5	3	
Size according to Figure	1	*9*	3	0	0	12
	2	1	*45*	1	0	47
	2 5	0	8	*29*	3	40
	3	0	0	1	*17*	18
No. patients		10	56	31	20	117

κ coefficient was 0.85, showing an "excellent agreement" between both measurements.[2]

Conclusions: This alternative method to determine LMA size appears to be useful when compared to the current "Gold Standard" (patient's weight). At present, we are comparing both methods in children undergoing general anesthesia, by assessing gas leak during mechanical ventilation.

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A.487 Sedation for paediatric endoscopic procedures: comparison of two techniques

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Background and Goal: Esophagogastroscopy and colonoscopy are a very useful diagnostic and therapeutic, yet invasive, procedure in the pediatric population Concerns regarding their performance include the need for sedation and analgesia, quality of conditions and recovery from the sedative agents. Most of these procedures are undertaken in an ambulatory environment thus emphasizing the importance of a swift recovery in the absence of side effects. Our work compares two of the techniques in use at our institution in the issues of safety, efficacy and suitability.

Materials and Methods: 100 children admitted to our facility were randomly assigned to two groups: group A received sedation with an intravenous Propofol infusion regime; group B received sedation with a combination of Meperidine and Midazolam intravenous titrated injections. Both groups were prepared similarly regarding fasting orders, monitoring and oxygen supplementation during the procedure. Data recorded included demographics, medication doses, procedure time, quality of procedure according to a score devised by Squires, Morriss et al.[1] and recovery time. Any complication or side effect was also recorded.

Results: Group A included 53 children aged 9 mo. to 12 years (median: 3 yrs), weights 7.2 to 35 kgs. (mean weight: 11.4 kgs.), a Propofol infusion started at a loading dose of 3 mgs /kg. followed by 6 mgs./kg./hr. was given using an automatic syringe pump (Graseby 3400). Procedure times ranged from 17 to 85 mins. (mean time 22 minutes), adequacy of conditions rated a mean of 1.2 (median 1) recovery times ranged from 7 to 23 mins. with a median of 16 minutes Side effects included transient mild hypoxemia (no less than spO2 89% for no more than 15 seconds) and a tendency to bradycardia (heart rate never less than 90 bpm). Group B comprised 47 children aged 2 to 14 years (median. 5 yrs), weights 11 to 50 kgs. (mean weight 27 kgs.), Meperidine and Midazolam were given intravenously in alternating, titrated doses up to 1 5 mgs /kg and 0.2 mgs./kg respectively Procedure times were 8 to 23 minutes (mean time 11 minutes), adequacy of conditions scored a mean of 1.6 (median 2), recovery times ranged 31 to 112 mins with a median of 65 minutes. Side effects included transient mild hypoxemia similar as that for group A and an increased rate of nausea and drowsiness.

Conclusion: The Propofol infusion regime demonstrated a better profile with improved adequacy of conditions (1 2 vs 1.6, $p < 0.05$) of procedure, faster recovery times (16 vs 65 minutes) and less nausea and drowsiness (2 vs 12). Procedure times were longer in group A probably due to more colonoscopy patients included in this group but this did not affect recovery times. Propofol infusion is a better choice for sedation in children undergoing ambulatory esophagogastroscopy or colonoscopy

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A.488 Is cooling essential in paediatric cardiac surgery? Clinical outcome after high-flow normothermic cardiopulmonary bypass

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Background: Hypothermia was first introduced in cardiopulmonary bypass (CPB) as a means of neuro-protection It is not physiological, causes impaired membrane function, ion pump inactivation, unfolding and denaturation of proteins, activation of Na-K ATPase, Ca ATPase, and impairs membrane function It worsens bleeding and pulm. compliance, with uncertain reduced risk of cerebral injury (1) It contributes marginally to improved myocardial protection over electromechanical quiescence (2)

Method: 70 consecutive surgical procedures were:

Simple· VSD (12), ASD (9), ASD + PS (1) Total = 22

Complex: TOF (6), AVSD (6), PA + VSD (5), Complex VSD (4), Mult. VSDs + RVOTO (4), PAPVC (4), MVReg (3), TGA (3), Tric Atr. (3), Ao Reg (2), DORV (2), PA + Intact V S (2), Conduit Obstruction (2), LVOTO (1), TAPVC (1). Total = 48

All surgery was performed on warm bypass with active warming to 37°C, flow rate of 3–3.5 $L/m^2/min$ Myocardial protection was with cold intermittent blood cardioplegia, and the haematocrit was maintained at 30%

Age 3 yrs 8/12 (2 mos–26 yrs) (median ((range))

Weight 11.95 Kg (3.8–58 Kg).

Ao. CC time 30′ (0–165′), CPBP time 94′ (28′–504′)

Results: *Excluding 4 patients who died.*

Time to.	Spont breathing	Extubation
<3 hrs	54 pts (81 81%)	28 pts (42 42%)
<24 hrs	85 pts (98 48%)	63 pts (95 45%)
>24 hrs	1 pt (1 51%)	3 pts (4 54%)

Use of Dobutamine 0–5 γ/Kg/min, 29 pts (43.9%)
5–10 γ/Kg/min, 6 pts (9.09%)
>10 γ/Kg/min, 1 pt (1 5%)
Other inotropes 16 pts (24.24%) Duration 1 day (3 h–7 days)
Periph. Temp. (6 hrs postop)· 36° C. (31–37.5°C)
Blood loss (Ir 6 hrs postop)· 10 ml/Kg (2 96–43 7)
$NaHCO_3$: 6 pts (9.09%)
Diuresis in 24 hrs (ml/Kg/hr)· 2.38 (0.9–6 19)
ICU stay: 1 day (1–13) HOSP. stay: 7 days (3–39)

Conclusion: We believe that *'warm body-cold heart'* surgery is an excellent technique with high flow CPB. Our patients had minimal bleeding, low use of inotropes, good renal & respiratory function and peripheral perfusion Although we do not have a long term neuropsychological evaluation, none of our patients developed major neurological deficits

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A.489 Low dose oral ketamine augments midazolam premedication in paediatric patients

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Background: Anxiolysis and sedation with oral midazolam are common practice in pediatric anaesthesia However, good or excellent results are seen in only 60–80% of cases (1) In our own patients presenting for dental repair, success rate is even lower (50%). For this reason, we asked in a prospective, randomized trial, if the addition of a low dose (2) of oral ketamine (MIKE: Ketamin 3 mg/kg, midazolam 0 5 mg/kg) results in a better premedication as compared to oral midazolam alone (MIDA, 0 5 mg/kg). We included 80 children (mean age 5 7 y, range 2–10), who underwent dental repair or strabism correction

Material and Methods: Upon approval by the local ethics committee and informed parental consent the children (ASA 1/11) were randomised into one of the study arms 20 min after oral premedication in the ward, the child's condition in the induction room was evaluated assigning 1 to 4 points to the quality of anxiolysis, sedation, behaviour at separation from parent and during venipuncture (with EMLA) On the 1st and 7th postoperative day, parents were interviewed for changes in behavior (eating, sleep, dreams, toilet training), recollection and satisfaction using a standardized questionnaire Evaluations used ANOVA and chi-square statistics

Results: Groups were similar with regard to age, sex, weight, intervention and duration of anaesthesia The results prior to Induction are given in the table: ("Success": Number of children with score 3 or 4, (). %success)

	Success Sedation	Success Anxiolysis	Success Separation	Puncture painless
MI	22/38	29/38	26/38	34/38
DA	(58)	(76)	(68)	(89)
MI	27/39	37/39	35/39	38/39
KE	(69)	(95)	(90)	(97)
	n s	p < 0 05	p < 0 05	n s

Apart from rare nystagm, no significant side effects (oxygen desaturation, hypersalivation, psychotic symptoms) were observed In the recovery room, no differences were found regarding sedation or time of possible discharge (ALDRETE Score ≥ 9). After 1 week, parents reported nightmares (MIDA 2, MIKE 2) restless sleep (6/9) or negative remembering (8/5). No substancial or continuing disturbances of behaviour or development were reported

Conclusion: Better anxiolysis and separation with ketamin plus midazolam were observed even in awake children (sedation not successful according to the preset criteria). The Increased success rate is of clinical significance The improvement was reflected in a lower stress factor for the inducing anaesthesist as evaluated by a VAS (1–10) (MIDA 2.8, MIKE 2.1, p = 0 1). The combination of both drugs in glucose sirup (pH 4 5 app) is chemically stable for 8 weeks (own data, remaining activity > 90% for both, HPLC)

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A.490 Efficacy and tolerability of tropisetron in the prevention of nausea and vomiting in children undergoing tonsillectomy and/or adenoidectomy

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Background and Goal of the Study: Nausea and vomiting are common problems after tonsillectomy[1]. Tropisetron, a new, long-acting 5HT3 antagonist has been found to be effective in preventing postoperative nausea and vomiting in adults[2] Its postoperative antiemetic effect in children is not yet well documented We studied the efficacy and tolerability of a single intravenous dose of tropisetron in preventing nausea and vomiting after tonsillectomy and/or adenoidectomy in children

Materials and Methods: With Hospital Ethics Committee approval and parental written informed consent we studied 98 children aged 2–12 years, ASA physical status I or II undergoing tonsillectomy and/or adenoidectomy in a prospective, randomised, double-blind, placebo-controlled study. Inhalational anaesthesia with Sevoflurane in N_2O/O_2 was performed After intubation Tropisetron 0.1 mg/kg (max 2.0 mg) or placebo was administered intravenously. Emetic episodes, need for rescue antiemetic treatment and analgesics were recorded for 24 hours after surgery Vital signs and sedation-scores were assessed in the first 4 postoperative hours Patient data were analysed using t-test and chi-square tests ($p = 0.05$).

Results and Discussion:

Vomiting episodes	Control	Tropisetron	p
None	17 (34 7%)	32 (65 3%)	<0 05
≥3	11 (22 4%)	5 (10 2%)	<0 0004
Need for antiemetics	14 (28 6%)	10 (10 4%)	<0 025

The only significant difference between the study groups was a slight predominance of males in the control group No difference could be shown between the groups for vital signs and sedation-scores Tropisetron significantly reduced postoperative vomiting and need for antiemetic medication during 24 hours No significant adverse effects of the study medication could be detected

Conclusion: One single intravenous dose of Tropisetron administered before surgery effectively reduces postoperative vomiting during 24 hours in children undergoing tonsillectomy/adenoidectomy

This research was supported by Novartis Pharma, Switzerland

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A.491 Intrathecal morphine for pain control in adolescents after scoliosis surgery

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Background & Goal of Study: Efficacy and safety in the control of postoperative analgesia is a difficult combination to reach in the pediatric population. The goal of our study is to evaluate the efficacy of low dose intrathecal morphine (0.01 mg kg^{-1}) and secondary effects in adolescent patients undergoing surgery for spinal deformities.

Material and Method: Between Feb-94 and July-97, 101 patients were prospectively enclosed The group was formed by 28 males and 73 females Age ranged between 11–19 years, the weight from 27–84 kg and the height 128–187 cm. In 73 cases was idiopathic scoliosis and 28 cases secondary scoliosis. Upon concluding spinal arthrodesis, the surgeon, under direct vision introduced the needle in L3–L4 or L4–L5 spaces The dose administered was 0.01 $\mathrm{mg.kg}^{-1}$, not exceeding 0 5 mg in total. To evaluate the results we gathered the following parameters: Time of opiate-dependent analgesia, the type of analgesic needed to pain control, the appearance of secondary effects, and the necessity of naloxone to treat it

Results & Discussion: The time of opiate-dependent analgesia ranged between 1 3 and 64 hours (23.1 ± 12 3). In 88.6% of cases, analgesia lasted more than 12 h. and in 40.4% exceeded 24 h Only 3 patients (2 9%) needed parenteral morphine; 64 (63.3%) required NSAID and 34 (33.7%) didn't demand any type of analgesic. Not one patient presented respiratory depression, somnolence, nor pruritus. 19 patients (18 8%) had nausea and 28 (27.7%), vomiting. Naloxone wasn't necessary in any case In multiple regression analysis there was no relation between time of analgesia and weight, height, type of scoliosis or total dose of intrathecal morphine Our results compare favorably with others studies[1, 2] that reported 18–36 h. Of analgesia.

Conclusions: Intrathecal morphine is safe and effective for the control of postoperative pain after surgery of spinal deformities Pain could be controlled by standard analgesics and parenteral opiates are avoided.

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A.492 Biblocks in congenital club foot surgery

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In most surgical procedures in paediatric orthopaedic practice regarding the lower limbs, regional anaesthesia is recognized as an effective method of providing analgesia in children The aim of this study is to show our experience in relation to regional anaesthesia in newborns and in children under six years of age, who should undergo surgery for the lengthening of Achille's tendon in club foot

Material and Methods: The present study was conducted, after obtaining parents' consent, on 32 children under six years of age with club foot who were divided into two groups· 21 children under 24 months (10 5 ± 1.7 ms) and 11 children over 2 years of age (4.6 plusmn; 1.0 ys), ASA I o II. Sleeping phase was obtained with intramuscular ketamine 7–10 mg/Kg, intramuscular atropine 0.02 mg/Kg and intravenous diazepam 0.2 mg/Kg. To guarantee the immobilization of the child during the operation, isolated doses of intravenous ketamine or diazepam 0.1 mg/Kg were administered. The performance of the biblocks (femoral nerve block and sciatic nerve block) (1) was obtained using not traumatic needles 20–21 G, 3.5 cm, connected to a neurostimulator Medival, set to 0 5–1 mA and 3 Hz (2). Isobaric Bupivacaine 0 25% was used as local anaesthetic and the total dose was of 2 5 mg/Kg.

Results and Discussion: All the 32 patients, under six years of age, who underwent surgery for congenital club foot were subjected to biblocks and the perioperative analgesia was excellent; all blocks were successful at the first attempt. Biblock technique guaranteed analgesia; furthermore it did not cause a motor block and all the discomforts related to it. A subarachnoid block or a general block were never necessary. There were no collateral effects due to the local anaesthetic. Postoperative analgesia was excellent. The analgesics was usually administered 12 hours after surgery. The oral hydration and the feeding were respectively begun 3 hours and 6 hours after the end of the operation.

Conclusion: B blocks in paediatric orthopaedic surgery can be considered a safe and good alternative to central blocks and general anaesthesia as it guarantees a good perioperative analgesia

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A.493 Infraclavicular block in children: is it an alternative to axillary block?

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Introduction: In October 1995 we introduced the infraclavicular block as an alternative for the axillary block. Our success rate was around 85%, comparable with the figures in the literature. The success rate for the supraclavicular block was around 97%. We looked for an alternative for the axillary block, something as good as the supraclavicular block, but without the dangers and complications of this block. We might have found it in the infraclavicular block

Technique: The patient is supine The arm may be in every position, as long as it comfortable for the patient The landmarks are clavicle, interscalene groove and the fold between arm and thorax. One draws a line from the interscalene groove to the end of the fold Halfway this line is the injection point. The needle must be introduced perpendicular to all planes The needle length has to be chosen to the size of the patient We use isolated needles with a nerve stimulator to find the nerves. In children one has to use a nerve stimulator for every peripheral block in children, because they will not tell you when they feel paraesthesia. We search for movements in the hand, forearm or shoulder/upperarm, or in the range of the ulnar, median and radial nerve.

Indications: All operations below the shoulder, with or without a bloodless field.

Results:

Year	Number	Comb anest.	Sedation	<2 years	<7 years	≥7
1995	29	8		1	5	23
1996	128	38	9	7	19	102
1997	65	13	5	6	12	47
	222	59	14	14	36	172

We had 9 partial blocks (failure rate 4%). This is much less than the figures of the axillary block This reaches the range of the figures of the supraclavicular block. We found a good alternative for the axillary block In fact is it a more universe block, while it can be performed with the arm in every for the patient comfortable position. The duration of the block varies.

Complications: We have had 1 clinical not significant pneumothorax. This was in the learning phase of this block.

Conclusion: The infraclavicular brachial plexus block is a good alternative to the axillary block, with a higher success rate It is a very useful block in children, because it is to perform independent of the position of the arm *and* the head.

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A.494 Caudal ropivacaine (0.25%) and bupivacaine for postoperative pain relief in children

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Background & Goal of Study: Ropivacaine is a new local anaesthetic agent and very similar to bupivacaine, structurally (1, 2). We aimed to compare the effects of caudal ropivacaine and bupivacaine on postoperative analgesia in children.

Materials & Methods: The study was performed in thirty four children, aged between 1 and 9, undergoing for elective inguinal hernia repaired after approval by the ethical committee. No premedication and analgesic drug were applied Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), peripheral O_2 saturation (SpO_2) and ECG were observed continuously in the operation room. Anaesthesia was obtained with halothane

(3%) and N_2O (67%) in oxygen and maintained with halothane (1–2%) and N_2O (67%) in oxygen Succinylcholine was administrated in patient who needed endotracheal intubation or muscle relaxation. At the end of the operation, all patients were taken in left lateral position and sterilized The patients were divided into two groups, randomly. Patients in group I (n = 17) received 0.5 ml/kg bupivacaine (0 25%) and patients in group II (n = 17) were applied 0 5 ml/kg ropivacaine (0 25%), caudally All patients were taken in postoperative recovery room following caudal application and turning off the anaesthesia The level of analgesia was assessed using paediatric objective pain score at 15th min, 1st, 2nd, 3rd and 4th hours postoperatively Bromage's modified motor block scale was used for the assessment of motor block

Results & Discussion: There was no difference between groups in weight and age POPS was not any differences between the groups at 15th min, 1st, 2nd, 3rd and 4th hours postoperatively POPS decreased at 1st and 2nd hours compared with 15th min value, however, there was no difference at 3rd and 4th hours. POPS was not higher than 5 point in any patients. Motor block was not seen. SAP, DAP and HR were the same in both groups No side effects related to local anaesthetic were observed in our patients

Conclusions: We concluded that ropivacaine (0 25%) is as efficacious as bupivacaine (0 25%) in producing postoperative analgesia for inguinal hernia

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A.495 Comparison of postoperative analgesia in children after continuous I.v. infusion of morphine or nalbuphine through a single-use infuser (Baxter)

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Background and Goal of Study: With this study we wanted to evaluate the efficiency of morphine or nalbuphine through continuous infusion in post-operative pain control during the 24-hours after Intervention. For this purpose we have used the Baxter Travenol Infusor [1]

Materials and Methods: In this study we included 60 children undergoing major orthopaedic surgery (duration 3–5 hours). For the Induction and maintenance of anaesthesia and the intraoperative analgesia we followed the same protocol for all children

At the end of the surgery and in the recovery room the children were assigned to two groups. Group A (n = 30) received I.V morphine 0.1 mg/kg as a bolus dose and was connected with NCA through an independent vein The elastic balloon was filled with morphine sulfate 20 μg/kg/h [2] diluted in 50 mls of D/5% with a flow of 2 ml/h. Group B (n = 30) received a bolus dose of 0 2 mg/kg of nalbuphine and the elastic balloon was filled with 0 05/kg/h nalbuphine [3] diluted in the same way as above.

Tropisetron (0 2 mg/kg-total dose 5 mg) was given IV to all children because of its antiemetic action.

Every six hours additional paracetamol (15 mg/kg) or proparacetamol (30 mg/kg) was given per os or I V

Every two hours we assessed the following parameters. pain scores, arterial oxygen saturation, consciousness level, respiratory rate, nausea and vomiting, urine retention. pruritus

Parametric data were analyzed using x-square test.

Results and Discussion: There were no significant statistical differences between the two groups. A mild to moderate pain was observed in two children of group A and three children of group B. Urine retention was observed in two children of group A and one of Group B Pruritus appeared in one child of Group A and in one of Group B

Constant infusion of both medicaments with a light, small device ensures constant plasma concentration, good analgesia and minimal side-effects

Conclusion: We recommend both methods as safe and effective for the control of post-operative pain

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A.496 Does propofol protect against postoperative vomiting after tonsillectomy in children?

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Background & Goal of Study: The goal of this study was to evaluate the antiemetic properties of propofol as a drug of induction in anaesthesia in tonsillectomies in children. We compared it to pentothal, a drug widely used by our practitioners for the same reason This study is part of a wider investigation still conducted in our department concerning postoperative nausea and vomiting in all paediatric surgical patients

Materials & Methods: 93 healthy children ASA I–II, aged 2–12, were randomly assigned to receive either propofol 2 5 mg/Kg or pentothal 5 mg/Kg as an induction factor All children were orally premedicated with diazepam 2 mg/Kg In both groups anaesthesia was maintained with oxygen-nitrous oxide and fentanyl 2 γ/Kg The mean age of the propofol group (A), (n = 49) was 6 44 with SD 3.04 and of pentothal group (B), (n = 44) was 5.68 with SD 2 82. The mean time of operation was in (A) group 19 21 min, SD 2 4 and in (B) group 21 45, SD 1.97. We used no antiemetic drugs Gastric contents were strictly aspirated in all patients after beginning and before the end of anaesthesia.

Paracetamol suppositories 30 mg/Kg were administered in all children while being in the recovery room

Results & Discussion: Vomiting was recorded for 24 h postoperatively by nursing stuff while subjects were in hospital and by parents after discharge from hospital. We found that 17 children of the (A) group and 19 from the (B) group vomited once or more times after surgery The difference between the two groups using the X^2 test was not statistically significant, $p > 0$ 05 Rescue antiemetics were administered when patients vomited more than twice This happened to two children of each group

Conclusions: We concluded that propofol as an induction factor is not an effective means of preventing vomiting after tonsillectomy in children compared to pentothal

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A.497 Incidence and therapy of midazolam-induced hiccups in paediatric anaesthesia

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Background: Rectal midazolam premedication is the golden standard in pediatric anesthesia (1) One of the side effects of this technique are hiccups, which can cause aspiration during mask-induction for general anesthesia (2), aspiration before or during rapid sequence intubation in emergency surgery or movements during diagnostic examinations (i e computertomography) Aetiology, Incidence and therapy of these hiccups are unknown. The goal of our study was to investigate a possible therapy of midazolam-induced hiccups by intranasal chlormethyl-spray application, which causes an intranasal cold stimulation, and a possible age or dose dependence of midazolam-induced hiccups.

Methods: After institutional approval and informed consent 100 children (ASA I, 3–15 kg) undergoing elective minor surgery were enrolled for the study. Group A was rectal premedicated with 0.5 mg/kg midazolam, Group B was rectal premedicated with 1 mg/kg midazolam If the children had hiccups during the following 20 min, we treated them with two short intranasal applications of chlormethyl-spray (Chlormethyl Dr Henning Spray™). The time from spray application to the possible interruption of the hiccups was measured All results were expressed as mean ± SD Statistical analysis was performed by ANOVA and Student's t-test. A $p < 0$ 05 was considered significant.

Results: We found 22% hiccups in group A and 26% in group B (n s) Time from rectal midazolam premedication to the first hiccup was 9 ± 5 min in group A and 12 ± 8 min in group B (n s). The intranasal chlormethyl-spray application (24 cases) was successful in 100% in both groups. We observed no side effects of our therapy Time from chlormethyl-spray application to interruption of the hiccups was 14 ± 23 sec in group A and 12 ± 11 sec in group B (n s) The mean age levels between children with or without midazolam-induced hiccups were 5 ± 9 months vs 21 ± 19 months in group A ($p < 0.01$) and 6 ± 7 months vs 20 ± 14 months in group B ($p < 0.01$).

Conclusions: The most important finding of our study is that intranasal chlormethyl-spray application is an effective therapy with no side effects for midazolam-induced hiccups in pediatric anesthesia The incidence of midazolam induced hiccups is high significantly age but not dose dependent. Because of the high incidence of midazolam induced hiccups intranasal chlormethyl-spray application is a possible therapy for this symptom in pediatric anesthesia

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A.498 Reinforced laryngeal mask airway for adenotonsillectomy in children: problems and comparison with tracheal intubation

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Background and Goal: Reinforced Laryngeal Mask Airway (RLMA) is an alternative to tracheal intubation for adenotonsillectomy With the laryngeal mask you do not need to use muscle relaxants and previous studies show less incidence of laryngeal spasm (1, 2). The aim of this prospective non randomized study is to evaluate the use RLMA for adenotonsillectomy in paediatric patients We will also compare the incidence of laryngeal spasm at the end of surgery in a group of intubated children.

Patients, Material and Methods: 30 consecutive children; 2 to 9 years (4.83 ± 1.95), 9 girls and 21 boys were included The retrospective control group included the last 16 children, 2 to 10 years (4.35 ± 1.87), 5 girls and 11 boys, that were intubated. Anaesthesia for both groups included. induction with sevoflurane, intravenous line: propofol 1 mg/kg, atropine 0.01 mg/kg and fentanyl 1–2 mcg/kg The control group also received succinylcholine 1 mg/kg for tracheal intubation. Maintenance of anaesthesia: nitrous oxide 50–66% and sevoflurane 2–3%. We studied in the control group the incidence of laryngeal spasm at the end of surgery. In the RLMA group we studied: problems with RLMA insertion (air leakage, cough, number of tries); problems with mouth gag insertion and during surgery (oxygen desaturation, airway obstruction or laryngeal spasm, RLMA displacement, surgical access) and problems at the end of surgery (airway obstruction or laryngeal spasm, cough). We compared the incidence of postoperative laryngeal spasm in RLMA and intubated children (Chi square, $p < 0.05$).

Results: Only one patient required reinsertion of RLMA; air leakage in one child before opening mouth gag; we had to relieve the mouth gag and open it again in four cases because the LM tube was in the middle of the mouth and in one case due to RLMA tube obstruction; only once the surgeon referred a difficult access related to a small oral cavity, RLMA displacement 2 cases; only one case of laryngeal spasm after RLMA removal. In the tracheal tube group the incidence of laryngeal spasm was 25% (4 of 16)

Conclusions: RLMA reduces the incidence of laryngeal spasm compared with tracheal intubation and is safe in adenotonsillectomy

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A.499 End-tidal and transcutaneous carbon dioxide monitoring during paediatric laparoscopic surgery

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Background: End tidal carbon dioxide (PetCO2) is monitored during paediatric laparoscopy to approximate arterial (Pa)CO2. A good correlation between PaCO2 and transcutaneous (Ptc)CO2 monitoring has been demonstrated during adult anaesthesia (1).

Goal of Study: To prospectively compare end tidal PetCO2 and PtcCO2 changes during paediatric laparoscopy in order to adjust ventilation

Materials and Methods: After institutional and parental approval, 21 ASA I–II children (2–14 yrs) were studied. Exclusion criteria were: cardiovascular, respiratory and haemoglobin diseases and morbid obesity. PtcCO2 sensor heated to 44°C (Kontron®) was applied above right claviocula. Children were induced with halothane (1.5–2.5 MAC) or with propofol and maintained with muscle relaxant, fentanyl and isoflurane (1.2–1.8 MAC) through endotracheal tube PetCO2 (Capnocap® Datex) was applied to every children. Their lungs were ventilated with FiO2 50% (air/O2) and a minute ventilation = [10 ml/kg frequency 10 ml/kg frequency adjust to the age]. Ventilator settings were kept constant during the study. Data were collected before CO2 peritoneal inflation (TO), 5 min after insufflation (T5), then every 10 min and at exsufflation (Texs) Data were analysed with ANOVA for repeated measures and Fisher's PLSD and expressed as mean ± SD with $p < 0.05$ significant. CO2 measurement techniques were compared with the Bland & Altman plot.

Results: Age was 7.2 ± 4.5 years and weight 30.2 ± 18.4 kg There is a significant increase of PetCO2 with time ($P < 0.05$) without any change of PtcCO2. The bias (comparison between the two methods) is 0.8 mmHg with agreement limits of –8 and 6.4 mmHg (bias ± 2SD).

	T 0	T 15	T 20	T Exs
PetCO2	30 ± 4.5	34 ± 6*	36 ± 5.5*	36 ± 7*
PtcCO2	29 ± 5	31 ± 6	33 ± 5.5	33 ± 7

Mean ± SD for PetCO2 and PtcCO2 (mmHg), * $p < 0.05$, vs T0

Discussion: It seems important to reconsider changes in PetCO2 as a non accurate estimate of PaCO2 When P(a-et)CO2 gradient becomes negative, PetCO2 overestimates PaCO2 (2) A range of 14 mmHg difference between the two techniques is of clinical importance. Adjustment of ventilator settings using only PetCO2 is inappropriate during paediatric laparoscopy; PetCO2 should be compared with PtcCO2 or PaCO2 to limit the risks of hyperventilation.

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A.500 A paediatric sedation unit in a university hospital: a one-year survey

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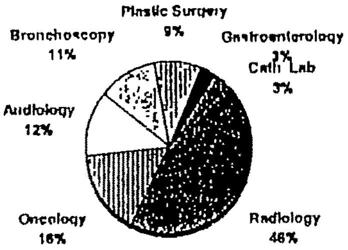
Background: Increases in diagnostic and invasive medical, surgical and radiological procedures in children have resulted in escalating need for anesthetic care in non-operating room locations We report the initial results of 1-year activity of our pediatric sedation unit

Materials and Methods: Between May 1996 and May 1997, ASA I–III patients, less than 18 years old, were sedated-anesthetized by our sedation team [composed of an anesthesiologist, specialist in pediatric anesthesia and a nurse anesthetist certified in pediatric intensive care] in remote locations: radiology (CT, MRI, radiation therapy, interventional radiology), oncology clinic, gastroenterology clinic, bronchoscopy suite, audiology and visual research institutes, cardiac catheterization laboratory (including electrophysiological studies), and pediatric plastic surgery clinic, in a 800-bed university hospital An anesthesia machine, scavenging suction, O2 source and routine monitors (pulse oximetry, ECG, automatic blood pressure, capnometer, precordial stethoscope, temperature) were available at all remote locations Following each procedure, recovery was managed in a suitable environment. The data was retrieved from our computerized database

Results: During this 1-year period, 1300 sedations-anesthetics were provided to 1100 patients aged 6 months to 18 years (mean ± SD = 5 ± 4 years). The average number of cases was 93/month. Average duration of cases was 60 min (range 30–120 min). ASA repartition was I (18%), II (76%), and III (6%) Radiology was the most involved department (44%), followed by the oncologic clinic (16%) (fig. 1). Propofol was the drug of choice in 55% of the cases whereas triclofos (27%) and midazolam (18%) were less used.



Conclusion: The creation of this pediatric sedation unit has offered the possibility of doing complicated cases, that were previously only done in the OR, in their natural environment. The increasing demand for remote sedation-anesthetics confirms the mutual satisfaction of physicians, nurses, technicians, parents, and above all children.

A.501 Physical and emotional conditions after ambulatory paediatric surgery: results of 413 questionnaires as part of postoperative quality assurance

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Day surgery is a small but growing part of medical care in the German health system To overcome traditional and still current objections quality control is an important tool. As a first step in the improvement of ambulatory care in our 600 bed city hospital we used a questionnaire to evaluate the incidence of typical postoperative complications and of short-termed behavioral changes.

Methods: Over a period of 12 months we asked the parents of 552 pediatric day care patients (age 6 m–12 y) to fill out a questionnaire 48 hours after treatment Midazolam 0.5 mg/kg (max. 15 mg) was given orally for premedication Anesthesia was provided for surgery in the ENT-, urological, dental (MKG) and surgical department. Induction was performed via inhalation (halothane, N_2O, O_2) or intravenously (thiopentone and suxamethonium/atracurium or propofol/remifentanil) and continued with halothane and N_2O/O_2 Paracetamol 30 mg/kg was given rectally as analgetic during the procedure and Nalbuphin 0.3 mg/kg was added intravenously in the PACU if necessary The patients were permitted to go home after they met our strict requirements for discharge.

Results: 413 questionnaires (74.8%) were returned Patients of the questionnaire-group were comparable to the whole population concerning age (4 9 ± 2.5 y vs 5 0 ± 2 5 y), weight (20.1 ± 9.0 kg vs 20 1 ± 8 6 kg) and premedication (0 42 ± 0.14 mg/kg vs 0 42 ± 0 14 mg/kg) The procedures were distributed as follows ENT 65 6%, surgery 10.4%, urology 13.3%, MKG 10.2%, others 0 5% Anesthesia was performed with endotracheal intubation in 86.2%, mask ventilation in 9.4%, laryngeal mask in 4.1% and ketamine iv in 0 2% Complications occurred intraoperatively in 4 cases (1%), but discharge home was not delayed and no patient had to be admitted for inpatient treatment At home treatment with analgetics was necessary in 34 6% (Paracetamol 88 4%, ASS 1 0%, others 10.6%). The general practioner or the hospital had to be contacted by 2 patients (1 persistent vomiting, 1 postoperative hemorrhage) after returning home 92 5% of all parents were satisfied with all aspects of their children's treatment and 7.5% were not. 91 3% would prefer a future surgical treatment on day care basis, 2 4% would prefer inpatient care and 6.3% couldn't decide

	PACU	Transfer	24 h	48 h
Nausea	21 3	10 4	8 2	0 2
Vomiting	16.2	10 4	14 8	0 7
Pain	44 3	35 8	50 1	22 5
Dizziness	31 5	19 6	3 6	0 0

Discussion: Postoperative nausea and vomiting were comparable with other publications (1, 2) The high incidence of pain until 48 hours postoperatively was the reason for an accurate revision of our analgetic regime. For better monitoring we introduced an additional phone call in the evening after surgery

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A.502 Adverse effects after paediatric magnetic resonance imaging

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Background & Goal of Study: To find out type, incidence and duration of adverse effects in children after anesthesia for Magnetic Resonancy Imaging (MRI) questionnaires were handed out to parents.

Materials & Methods: MRI examinations in anesthesia (duration 46 ± 16 min; 23–155 min) were performed in 140 children (mean age 3.75 ± 2 8 years; 6 days–13 yrs) After premedication with midazolam (0.1–0.2 mg/kg BW iv) and atropine (0 01 mg/kg BW iv.) anesthesia was induced with thiopental sodium (5–8 mg/kg BW iv.) Maintenance was done with isoflurane (0.6–1 0 Vol%) in 77 children (55%), sevoflurane (0 7–1.0 Vol%) in 36 children (25.7%), desflurane (1–3 Vol%) in 14 children (10%), and halothane (0 6–0.8 Vol%) in 12 children (8 6%) in an oxygen/air mixture (FiO_2 = 0 4; flow 51/min) using an open mask in supine position In each patient a conventional multiparametric cardiorespiratory monitoring was performed [1] 0.1 mmol/kg BW Dimeglumingadopentetat was used in 60 children (43%) as contrast agent Questionnaires about postanesthetic adverse effects within the first 72 hours were handed out to 201 parents For statistics contingency analysis was used.

Results & Discussion: Responses were received from 140 parents (69 7%) out of 201 Adverse effects were reported for the time of 1 hour (n = 54), 24 hours (n = 25), and even 72 hours (n = 19) after MRI examination. Solitaire adverse effects were found in 68, combined in 25 children. In 66 children different adverse effects were reported: restlessness (n = 28), nausea (n = 18), vomiting (n = 17), singultus (n = 11), conjunctival injections (n = 10), rhinitis (n = 8), diarrhea (n = 7), tiredness (n = 7), rash (n = 7), dizziness (n = 4), headache (n = 2), flatulence (n = 2), abdominal pain (n = 1), fever (n = 1), laryngitis (n = 1), asthma (n = 1) None of the inhalational agents showed a statistical significance in the incidence of adverse effects [2].

Conclusions: MRI examinations induce a high variance of adverse effects More than one adverse effect is possible, the appearance is not predictable and occurs within the first 72 hours of observation time To evaluate whether anesthetic or contrast agents cause the adverse effects, further studies are necessary Parents should be informed about the increased incidence of adverse effects after diagnostic procedures for MR Imaging in anesthesia

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A.503 Tonsillectomy for children: evaluation for ambulatory practice

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Goal of Study: is to evaluate the safety of ambulatory anaesthesia (1) in tonsillectomy considering monitoring criteria six hours pre and postoperative.

Materials & Methods: This prospective study concerns 206 children ASA I having tonsillectomy. The average age is 5 ± 2 6 years All of them were premedicated with midazolam given orally or rectally The induction was either by inhalation of halothane or intravenous injection of propofol All children had an intravenous line, were orotracheally intubated and manually ventilated Fentanyl (2 µg/kg) was only given to 56% of them Maintenance of anaesthesia was provided by inhalation of halothane or isoflurane in 50% gaz mixture Heart rate, blood pressure and SaO_2 were monitored all through the surgery and in PACU The anaesthesia's average time was 23 ± 14 min Two surgical techniques were used· the guillotine tonsillectomy for 86% and the dissection for 14% Postoperative analgesia was conducted by diclofenac rectally and intravenous propacetamol immediately postoperative, repeated four hours later, then taking over with paracetamol rectally Early postoperative detection of respiratory, bleeding complications as well as monitoring of pain (C H E.O P S 's scale) and vomiting were recorded during the first hour (H), every hour during six hours and every two hours during the first twenty-four hours postoperative

Results and Discussion:

In PACU	≤H6	>H6
Desaturation 22		
Vomiting 14	vomiting 61	
Bleeding with revision 2	bleeding with revision 5	bleeding with revision 1
	without revision 5	
Week pain 105	great pain. 7	pain with revision 1

Children with no complications during the first six hours did not have complications beyond the sixth hour

Conclusion: In tonsillectomy, children without morbidity during the first six hours postoperative (87%) could be the subject of an ambulatory anaesthesia, provided that strict monitoring protocole is used

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A.504 Evaluation of sevoflurane anaesthesia for children requiring cardiac catheterization

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Background and Goal of the Study: General anaesthesia for cardiac catheterizations for children with congenital heart diseases is a real challenge Sevoflurane (S) which allows inhalation induction and a rapid return to consciousness combined with few cardiovascular effects 1 might well be useful. We assessed the characteristics of anaesthesia using S in this indication.

Patients and Methods: After explanation and agreement from the parents, 40 consecutive child patients aged 4 months to 10 years who were scheduled for cardiac catheterization were anesthetized according to a standardized protocol 0.35 mg/kg intrarectal midazolam and application of EMLA 1 h before the procedure ECG monitoring, noninvasive arterial pressure, SpO2. Induction by inhalation with 8% S in a mixture of air + O2 (FiO2:0.21) (TO) After the eyelash reflex disappeared (T1) the concentration of S was lowered to 3 5% until a laryngeal mask was inserted (T2). A venous line was installed (G5%, 10 ml/kg/h) The concentration of S inhaled was then kept at between 1.5% and 3% with O2 + air (FiO2 0 21) depending on movement or no movement occurred to stimulus At the end of the procedure, administration of S was stopped when vascular compression ended, after withdrawal of the introducing devices. The times (T0–T1), (T0–T2) and the times between interruption of S and eyes opening, removal of the laryngeal mask and the first cry, together with the time at which the child left the recovery room were assessed. All the side effects during induction, procedure and recovery were noted The results are expressed as means ± SD.

Results and Discussion: 18 boys and 22 girls, mean age 3 years 3 months ± 2 years 8 months were anesthetized using this protocol The times T0–T1 and T0–T2 were respectively 34 ± 8 s and 217 ± 35 s The side effects to induction were· cough (2), brief agitation (5), apnea (8) of which 5 resulted in a drop of SpO2 > 5% of initial value, requiring manually assisted ventilation. The facial mask was always remarkably well accepted The mean duration of anesthesia was 57.5 ± 13 min and the mean concentration of S inhaled during catheterism was 2 1 ± 0.4%. The changes in arterial pressure and levels of ETCO2 never exceeded ± 20% of the base values. In 5 cases desaturation was observed during catheterism corrected by enriching the 02 content of the mixture inhaled. Recovery time was 6.3 ± 2 1 min for ablation of the laryngeal mask, 7.1 ± 3.5 min to the first cry and 8 4 ± 3.8 min to eyes opening. On average 12.5 ± 4 3 min after S ceased to be administered, all the children presented PACU discharge criteria. The side effects observed during recovery are headache 4, cough 2, agitation 2, shivering 1

Conclusion: Sevoflurane has few negative inotropic effects and provides very rapid loss and recovery of consciousness, so would seem to be well indicated for carrying out general anesthesia for diagnostic or interventional cardiac catheter procedures in young children with congenital heart diseases.

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A.505 Spontaneous recovery of neuromuscular transmission after mivacurium in children under balanced, halothane and isoflurane anaesthesia

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Volatile anaesthetics significantly potentiate the neuromuscular (n-m) block produced by mivacurium (MIV). MIV requirement under halothane and isoflurane [1] anaesthesia is by 1/3 to 2/3 lower than under balanced anaesthesia, one may therefore expect that the presence of volatile anaesthetics may slow down the recovery from the n-m block.

Methods: With approval from the Institutional Ethics Committee and parental consent, 29 children (2–12 years old, ASA PS group I-II) scheduled for surgical procedures not exceeding 90 min were studied They were assigned at random to receive N_2O/O_2 narcotic (BAL), N_2O/O_2-halothane (HAL) or N_2O/O2-isoflurane (ISO) anaesthesia MIV, 0.2 mg kg^{-1} was given to facilitate intubation and MIV infusion was used during the surgery. The n-m block was allowed to resolve spontaneously. The n-m transmission was monitored by recording EMG activity of the adductor pollicis in the response to the supramaximal stimulation of the ulnar nerve at wrist with repetitive trains-of-four, 2 Hz for s, at 10 s intervals. Core body temperature was kept above 36°C. IPPV was used and normocapnia was maintained. End-tidal concentration of anaesthetics was and maintained at 1 MAC level throughout the procedure until the first twitch response (T_1) recovered >95% and TOF ratio (T_4/T_1) >90%. The time of the T_1 recovery from 25% to 75% (RF_{25-75}) and the time from the T_1 recovery from 10% to TOF ratio = 70% (T_{10}-$TOF_{70\%}$) were measured. ANOVA was used and p < 0.05 was considered significant)

Results: The study groups were similar in the respect of age and body weight. The parameters describing the recovery the neuromuscular transmission are summarised in the table.

	BAL n = 10	HAL n =.10	ISO n = 9
RF_{25-75} (min)	4 3±2 2 [1.5–0 3]	5.3±1 2 [3 5–0 2]	5 3±1.4 (NS) [4.2–7 2
T_{10}-TOF_{70} (min)	8 1±3 3 [3 3–14 8]	9.9±2 4 [6 2–14.6]	11 5±3 8 (NS) [6 0–18 2]

Values are given as mean (±SD) and [range]

Conclusions: Even though the recovery of the n-m transmission takes a little longer in the presence of volatile anaesthetics than under balanced anaesthesia, it remains short and reliable. It seems that the spontaneous recovery from the n-m block produced by mivacurium can be allowed even in patients anaesthetised with halothane or isoflurane

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OBSTETRIC ANAESTHESIA

A.506 Determination of the minimum local analgesic concentration of epidural ropivacaine in labour

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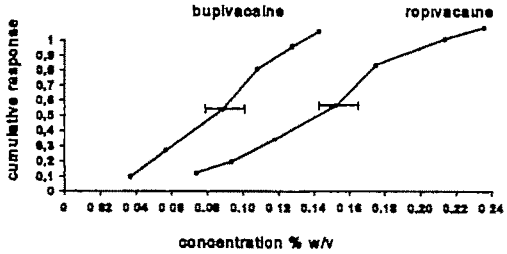
Background: The concentration of ropivacaine to be used for labor analgesia has been arbitrary decided[1, 2]. A clinical model was devised to determine the effective local anesthetic concentrations in 95% (EC_{95}) as well as in 50% of patients (EC_{50}) and EC_{50} was defined as the minimum local analgesic concentration (MLAC)[3]. The aim of this study is to determine the MLAC of ropivacaine and to determine the relative analgesic potencies of bupivacaine and ropivacaine for labor analgesia.

Methods: After Institutional Ethical approval, 88 healthy primiparus women, at more than 37 weeks gestation requiring epidural analgesia for labor pain were enrolled in the study. After epidural catheter placement, 20 mL of the local anesthetic solution being tested was given. The concentration was determined by the response of the previous patient to a higher or lower concentration using double-blinded, up-down sequential allocation. Efficacy was assessed using a 100 mm visual analogue pain scores (VAPS) scale with less than 10 mm within 1 hour defined as effective MLAC was determined by the Dixon and Massey formula[4].

Results: No differences were noted in demographics. Of the 44 women entered into the ropivacaine group, 4 were rejected, leaving 40 for analysis. MLAC of ropivacaine was 0.156% (95% CI 0 136 to 0.176) Of the 44 women entered into the bupivacaine group, 3 were rejected, leaving 41 for analysis. MLAC of bupivacaine was 0.093% (95% CI 0 076 to 0 110). (MLAC of ropivacaine vs: bupivacaine P < 0 0001, 95%CI 0.036 to 0.090). The concentration response plots are reported in the figure. Relative median potency of ropivacaine to bupivacaine was 0.60 (95%CI 0 42 to 0 77). Molar EC_{50} (MLAC) was 5.02 mmol/L (95% CI 4.37 to 5 66) for ropivacaine and 2.86 mmol/L (95% CI 2.33 to 3.38) for bupivacaine Molar potency ratio was 0.57 (95% CI 0.40 to 0 74)



Conclusions: Ropivacaine is significantly less potent than bupivacaine. By using the MLAC data it should be possible to optimize the concentration of local anesthetic to provide the greatest effect at the minimum disadvantage.

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A.507 A comparison of ropivacaine 0.10% and sufentanil 10 μg with ropivacaine 0.20% for epidural labour analgesia

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Background: The addition of opioids to local anesthetic for labor analgesia is a well established technique. In this study we evaluated the effects of the addition of sufentanil to ropivacaine for epidural labor analgesia.

Methods: Forty nulliparous parturients, with uncomplicated pregnancies and a cervical dilatation at 2 to 5 cm were randomly allocated to receive epidural analgesia with 20 mL of ropivacaine 0.20% (n = 20) or ropivacaine 0.10% plus 10 μg of sufentanil (n = 20). Monitoring of FHR and uterine activity was started at least 10 min before induction of epidural block. Maternal blood pressure, HR and SaO_2 were monitored before induction and every 5 min. Pain of contractions was assessed on a 100-mm visual analogue pain scale (VAPS) every 5 min Onset time was defined as the time from the injection to pain relief (with a VAPS at least <20). Duration of action of each dose was defined as the time from injection to request for further pain relief Statistical analysis was performed using unpaired t-test or Mann Withney U-test, where appropriate.

Table 1

	Ropivacaine 0 20%	Ropivacaine 0.10% with 10 μg sufenta
Onset of analgesia (min)	18 2 (3 5)	15 5 (3.5)
Duration of analgesia (min)	130 (9 7)*	101 (26 7)

*P < 0.0001, t-test

Results: The two groups were comparable with regard to age, weight, height, cervical dilatation and VAPS before epidural. The analgesia was satisfactory in all cases. Analgesia was significantly longer (P < 0.0001) with the higher concentration of ropivacaine In the 0.20% ropivacaine group, five parturients have moderate hypotension (<90 mmHg) and one patient had severe and prolonged hypotension requiring i.v. ephedrine Only patients who received sufenta had transient, moderate pruritus The lower concentration of ropivacaine allowed for ambulation in all cases while only four patients receiving the higher concentration were able to walk alone.

Conclusions: The addition of 10 μg of sufenta to 0.10% ropivacaine produced a maternal analgesia similar to that produced by 0 20% ropivacaine with a similar onset time Although the duration of analgesia was approximately 30 minutes longer with 0 20% ropivacaine, patients receiving 0 10% ropivacaine and sufenta were able to walk and had less hypotension and these features may be of great advantage for labor analgesia

A.508 Ropivacaine 0.10% plus sufentanil and bupivacaine 0.0625% plus sufentanil are equianalgesic mixtures for epidural analgesia during first stage of labour

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Background: On the basis of a previous study we determined that the ropivacaine bupivacaine potency ratio is 0 60 (unpublished study) In this study we evaluated the analgesic effects of two equianalgesic concentrations of ropivacaine and bupivacaine during the first stage of labor.

Methods: 44 nulliparous parturients, with uncomplicated pregnancies and a cervical dilatation at 2 to 5 cm were randomly allocated to receive epidural analgesia with 20 mL of 0 10% ropivacaine and 10 μg of sufentanil or 0.0625% bupivacaine with 10 μg of sufentanil Monitoring of FHR and uterine activity was started at least 10 min before induction of epidural block Maternal blood pressure, HR and SaO_2 were monitored before induction and every 5 min Pain of contractions was assessed on a 100-mm visual analogue pain scale (VAPS) every 5 min. Onset time was defined as the time from the injection to pain relief (with a VAPS at least <20) Duration of action of each dose was defined as the time from injection to request for further pain relief

Table 1

	Ropivacaine	Bupivacaine
Onset (min), mean (sd)	14 5 (2 9)	18 3 (7 6)
Duration (min) mean (sd)	100 (25 4)	96 5 (31)
Ability to walk (n of patrunents)	44 (100%)	44 (100%)

Results: The two groups were comparable with regard to age, weight, height, cervical dilatation and VAPS before epidural The analgesia was satisfactory in all cases Median values of VAPS were comparable during the period of observation. There was no lower limb weakness and the parturients were able to walk without difficulty. Non changes in FHR were detected. No maternal hypotension was observed.

Conclusions: According with the potency-ratio, the two concentrations examined were equianalgesic in potency and duration Further studies are in progress to evaluate the use of a such ultra-low concentration of ropivacaine for epidural continuous infusion.

A.509 Epidural analgesia, progress of labour and maternal motor blockade. A comparison of ropivacaine and bupivacaine

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Aim of the Study: Aim of this study was the evaluation of the efficacy of peridural analgesia with ropivacaine and bupivacaine in different concentrations during labour and delivery, with reference to the progress of labour.

Materials and Methods: By previous informed consent and request, 75 women received peridural analgesia for labour and delivery, they were divided in 5 groups

Group 1 Bupivacaine 0 125% 10 ml bolus and infusion rate of 5 ml/h;

Group 2: Bupivacaine 0 125% 15 ml bolus and infusion rate of 10 ml/h;

Group 3; Ropivacaine 0.2% 10 ml bolus and infusion rate of 5 ml/h,

Group 4: Ropivacaine 0.2% 10 ml bolus and infusion of ropivacaine 0.1% at the rate of 10 ml/h;

Group 5: Ropivacaine 0.2% 10 ml bolus and infusion of a solution with ropivacaine 0.75 mg/ml at the rate of 10 ml/h.

We evaluated: The analgesic efficacy using VAS 30 minutes after the onset of infusion and during fetal expulsion, bromage scale and the onset of paresthesia, the length of fetal expulsion and the necessity of ventouse extraction delivery.

Results:

Every group showed apgar scores and the data on the progress of labour of complete safety The best results on analgesic efficacy were obtained by groups 2 and 5, with the difference that in group 5 motility was not so affected as in group 2. Excluding the data about cesarean sections, all the groups with ropivacaine have a lower rate of ventouse extraction delivery and better score of bromage scale.

Conclusions: In every group satisfactory results were obtained. The results of the present study seem to point out a good analgesic efficacy of ropivacaine with a lower motor blockade than bupivacaine Further studies would be appropriate for evaluating the higher rate of vomiting and nausea in the groups treated with ropivacaine.

A.510 Ropivacaine 2 mg/ml *vs* ropivacaine 1 mg/ml + sufentanil 0.2 μg/ml for extradural analgesia in labour

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Background and Goal of the Study: The recommended ropivacaine concentration for the maintenance of épidural labor analgesia is 2 mg/ml, using 6 or 8 ml/h The purpose of this randomized study was to compare ropivacaine 2 mg/ml with ropivacaine/mg/ml + sufentanil 0 2 μg/ml used for the maintenance of analgesia

Materials and Methods: 25 healthy parturients with singleton, uncomplicated pregnancies, in active labor were included after the epidural analgesia induction with ropivacaine in sufficient amount to obtain a good quality of analgesia The parturients were randomly allocated to one of the two groups to receive continuous extradural infusion either ropivacaine 2 mg/ml or ropivacaine 1 mg/ml + sufentanil 0.2 μg/ml. The continuous extradural infusion rate in both groups was 6 ml/h if the woman was less than 160 cm tall and 8 ml/h if she was more than 160 cm Additional boluses of 5 ml of ropivacaine 2 mg/ml were injected if necessary Visual analogic pain score, dilatation, analgesia sensory level and degree of motor block were measured at the beginning of continuous infusion, 30 mn later and hourly to the beginning of expulsive efforts Maternal satisfaction was assessed when the analgesia was achieved and the lumbar catheter withdrawn

Results and Discussion: The two groups were comparable concerning age, height and term Maintenance dose of ropivacaine was higher in the 2 mg/ml group 97 17 mg versus 69 27 mg ($p < 0.05$) Visual analogic pain score at any time was not statistically different between the two groups But, the last one before delivery was higher in the 1 mg/ml + sufentanil group The mean superior sensitive level was comparable in the two groups (mean level = T9). There were more motor blocks in the 2 mg/ml group 4/12 versus 1/11 ($p > 0\ 5$) and one of the women in the 2 mg/ml group has a Bromage score egal to 2. Maternal satisfaction scores were not statistically different between the two groups

Conclusion: Ropivacaine 1 mg/ml + sufentanil 0.2 μg/ml seems to be adequate during labor analgesia, and permit to use less local anesthesic But, ropivacaine 1 mg/ml + sufentanil 0 2 μg/ml is inadequate for the second stage of labour and needs an additional bolus just before expulsive time

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A.511 Minimum local analgesic volume for epidural bupivacaine 0.125% in labour

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Background and Goal of Study: Epidural analgesia in labour with plain bupivacaine 0.125% is associated with a significant failure rate[1]. And yet this is a concentration that lies on the flat upper part of the dose response curve for epidural bupivacaine [2], implying that it should be effective in most instances.

We performed this study to examine the role of bolus volume in pain relief in labour with bupivacaine 0.125%

Materials and Methods: Ethics approval and informed consent were obtained 50 women requesting epidural pain relief in labour were recruited The syringe volume of the initial bolus was decided by double blind up and down sequential allocation using a 1 ml dosing interval No test dose was given, and the first woman received an arbitrarily chosen 15 ml bolus Opaque syringes were used. Efficacy was accepted if visual analogue pain score (VAPS) fell to 10 or less within 30 minutes.

Results:

Age	Mean (SD)	27 7 (6 7)
Weight	Mean (SD)	77 9 (15 1)
Height	Mean (SD)	163 4 (5 7)
Gestation	Med (IQR)	40 (40–41)
Nullips	Count	27
Cervix	Median (IQR)	2 (2–3)
Initial VAPS	Median (IQR)	70 (57–84)

The effective volume in 50% of the women studied was 17.7 ml (95%CI 15 2–20.2).

Discussion: Our findings suggest that previously reported failures of analgesia with plain bupivacaine 0 125% w/v were due to inadequate volume

17 7 ml of 0 125% w/v contains 22 mg bupivacaine. The same analgesic point can be achieved with 20 ml 0.07% w/v [2], which contains 14 mg bupivacaine. Plain bupivacaine 0.125% is not an efficient solution for use in epidural pain relief in labour.

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A.512 Patient-controlled analgesia: extradural fentanyl and intravenous morphine compared after Caesarean section

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Background and Goal of Study: Following Caesarean section patient-controlled extradural fentanyl (PCEF) has been found to produce effective analgesia with a remarkably low incidence of nausea and vomiting (1, 2). This study was designed to compare PCEF with patient-controlled intravenous morphine (PCIM).

Materials and Methods: After ethical approval, 84 ASA I–II women having an elective Caesarean section in the morning, under a standard combined intrathecal and extradural (CIE) anaesthetic, were entered into this randomised, double-blind, study. Patients were attached to both extradural and intravenous patient-controlled analgesia (PCA) devices in the recovery room. The extradural PCA device was programmed to allow a 5 ml bolus with a 10 minute lockout interval and the intravenous PCA device to allow a 0.5 ml bolus with a 5 minute lockout. Group PCEF received extradural fentanyl 4 μg/ml and intravenous normal saline. Group PCIM received extradural normal saline and intravenous morphine 2 mg/ml. Patients were told to use both PCA devices. Patients were assessed in recovery, at 4 h and 8 h after delivery, at 2300 and at 0800. Mann-Whitney and Kruskal-Wallis tests were used to analyse data

Results and Discussion: Groups PCEF (n = 42) and PCIM (n = 42) were matched. All patients received rectal diclofenac at operation. PCEF patients used a median of 18 μg/h (interquartile range (IQR) 11–32) of fentanyl. PCIM patients used 1.7 mg/h (1 2–2 4) of morphine The mean hourly volume of intravenous PCA solution delivered was 41% lower for PCEF than for PCIM patients (P = 0.002). Pain scores were lower for PCEF at 4 h, 8 h and 0800 The highest pain score (VAS 0–100 mm) experienced at rest for PCEF patients was median 19 (IQR 10–33) compared to 32 (14–52) for PCIM patients (P = 0 02). On coughing the highest score was 31 (21–41) for PCEF compared to 56 (31–71) for PCIM (P = 0.0003) There was less Nausea (N) and vomiting (V) with PCEF (N = 14%, V = 2%) than with PCIM (N = 33%, V = 12%) (P = 0.03). There was also less drowsiness with PCEF from 8 h onwards; this was most marked at 0800, when 14% were drowsy with PCEF compared to 58% with PCIM (P = 0 0002). Pruritus was similar with both regimes.

Conclusion: PCEF produced more effective analgesia, with less nausea, vomiting and drowsiness, than PCIM We consider it to be a practical alternative to PCIM

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A.513 Effect of fluid preload on coagulation as measured by thromboelastography

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Background and Goal of Study: During pregnancy, thromboelastography (TEG) shows a hypercoagulable state [1]. Moderate haemodilution also enhances coagulation We studied the effect of preloading patients presenting for caesarean section on TEG parameters.

Materials and Methods: After informed consent and ethical committee approval, we performed TEG on 20 patients undergoing caesarean section with spinal anaesthesia, before and after infusion of 500 mls of colloid. Data was collected and analysed using an SPSS computer package

Results:

	Mean Diff	95% CI	Sig
R time	6 85	0 35, 13 35	0 04
K time	3 80	1 51, 5 48	0 02
R + k time	10.35	2.39, 18 30	0 013
α angle	−7.00	−12 9, −1 13	0 022
MA	0 675	−4.03, 5 38	0 767

Discussion: We have found small but statistically significant changes in TEG variables that indicate that preloading patients enhances coagulation. This has been reported in in-vitro studies [2], and also in in-vivo studies in patients undergoing general surgery [3] It is not clear whether these changes are clinically relevant.

Conclusion: This in-vivo study agrees with published in-vitro studies of the effect of preload on TEG. Preloading induces a hypercoagulable state

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A.514 Effects of the Valsalva manoeuvre on the cerebral circulation in pregnancy

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Background and Goal: The Valsalva manoeuvre (VM) has been used to assess cerebral autoregulation in volunteers Labour often involves periods of straining similar in nature to VM. This study was designed to investigate the changes in cerebral blood velocity during the VM and to explore its potential use for the evaluation of cerebral autoregulation in late pregnancy.

Materials and Methods: With local ethics committee approval and informed consent, 7 healthy pregnant women (>34 weeks gestation) were recruited. All patients had their arterial blood pressure (Finapress, Ohmeda, USA) and blood velocity in the middle cerebral artery (Vmca) continuously monitored The Vmca was measured using a 2 MHz transcranial Doppler probe (DWL, Sipplingen, Germany) which was fixed in position throughout the study period. After adequate instruction and a period of stable arterial and Vmca reading, patients were asked to perform 3 VMs. The VM were performed in a semi-recumbent position by taking a deep breath and forcefully exhaling against a closed valve connected to an anaeroid pressure gauge aiming to maintain a pressure of 30 cm water for 15 seconds. Changes in Vmca and mean blood pressure (MAP) during phase II and IV of the VM were used to calculate autoregulation indices (AR-II and AR-IV respectively) previously described.[1]

Results and Discussion: The main findings of this study are outlined in Table 1. The autoregulatory response to the valsalva maneuver in pregnant patients was lower than reported in the non-pregnant patient.

Possible indices of autoregulation

	AR-II	AR-IV
Pregnant	1 14 ± 0 44	1 07 ± 0 11
Non-pregnant	2 87 ± 1 3	1 36 ± 0 25

All values are mean ± SD.

Conclusions: Analysis of VM in pregnancy provides important information about cerebral autoregulation. This may be of value in assessing cerebral haemodynamics in pregnancies complicated by neurologic abnormalities such as pre-eclampsia.

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A.515 Vascular effects of propofol and thiopentone in the isolated perfused human placental cotyledon

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Background: Concucting intravenous general anesthesia to women during pregnancy as well as for cesarean sectio, thiopental has for years been the well-established drug of choice (1). Since late eighties, propofol has gained use for the same purposes. We studied the effect of propofol and thiopental on the vasculature in the isolated perfused human placental cotyledon.

Materials and Methods: Placentas were obtained from 24 healthy women, all having had an uncomplicated pregnancy and a normal vaginal delivery. In two intact cotyledones the artery and the corresponding vein were cannulated, enabling as well perfusion of the fetal compartment of the cotyledones as monitoring the arterial pressure. Perfusion was started within 15 minutes of vaginal delivery of the placenta, using an aerated modified Krebs-Ringer solution. Perfusional flow rate was adjusted to a stable arterial pressure of 20–30 mm Hg. Preconstriction were done in half the experiments by continuous infusion of Thromboxane (U46619), achieving a stable arterial pressure 200–250% of the above resting pressure. Propofol and thiopental were administered by continuous infusion of incremental doses in 12 experiments each, half of these preconstricted

Results: Neither propofol nor thiopental had any effect on perfusion pressure in the non-preconstricted cotyledones. In the pre-constricted cotyledones perfusion pressure was reduced significantly by thiopental 32 yg/ml or propofol 4 yg/ml ($p < 0.05$, Mann-Whitney). Both concentrations are very high in the clinical relevant interval, but may both be reached in induction(2, 3)

Conclusion: This in vitro study suggests high concentrations of thiopental and propofol to exert a dilatational effect on the feto placental vasculature, if preconstricted by thromboxane

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A.516 Incidence of fetal acidaemia after spinal anaesthesia for elective Caesarean section – a persistent trend in the midnineties?

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Introduction: With an increasing frequency of Spinal anesthesias (SPA) for elective Cesarean sections the incidence of severe fetal acidemia also increased in a Swiss epidemiological study (1) One may argue that such historical data are biased and anesthesia care in the past was not consistent with recent standards of care. Therefore data from 1995 and 1996 were analyzed to see if this trend is consistent

Patients and Methods: The presented epidemiological study used data of the Swiss obstetric study group After exclusion of all cases with extraneous factors that may have affected the health of the neonate, umbilical artery pH, Apgar score, and other neonatal outcome measures with reference to anesthetic technique were analyzed The goal of the data filtering procedure was to eliminate all factors which could have influenced the choice of the anesthesia technique. Gestational age had to be between 37 and 42 weeks The Relative Risk of fetal acidemia and the Odds Ratio were calculated using the patients having c-section under general anesthesia as reference. For both parameters the 95% confidence interval was calculated In addition to the pH-values the neonatal well-being was analyzed similarly. P values of less than 0.05 were considered significant

Results: 1445 elective cesarean sections of the 75464 recorded deliveries entered the analysis (792 SPA, 406 Epidural anesthesia (EDA); 247 general anesthesia (GA)). The frequency of fetal acidemia ($pH < 7.10$) was significantly increased in the SPA group: Odds-Ratio 5 35 (95% Confidence Interval 1 82–17.7) compared to GA Apgar Scores and other measurements of neonatal well-being did not differ in all three groups.

Conclusion: The risk of severe fetal acidemia is clearly elevated after elective cesarean delivery after spinal but not epidural anesthesia compared to GA. It is not clear at present what possible causal relationship could exist between SPA and fetal acidemia.

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A.517 Influence of urodilatin on perfusion pressure in pre-eclampsia. A study of the placental model *in vitro*

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Background & Goal of Study: The hypothesis that preeclampsia may be associated with an increase in the response of the placental arteries to vasoconstrictors is well known (1). Preeclampsia is characterized by hemoconcentration and plasma volume depletion It may alter atrial natriuretic peptide (ANP) mechanisms of liberation (2) Urodilatin (URO, CDD/ANP-(99–126) is a new member of the natriuretic peptide family isolated from human urine Intravenous URO infusion may be useful in treatment the preeclamptic hemodynamic changes in placental circulation. The goal of this work was to compare the perfusion pressure changes induced by URO in placentas from normal and preeclamptic pregnancies

Material & Methods: Placentas obtained from 12 nulliparas (6 cases of preeclampsia and 6 uncomplicated pregnancies, control) after elective cesarean sections, were perfused in vitro using modified Cedard manner Perfusion pressure, measured continuously, was the main parameter of changes in vascular status over 120 min period. Concentration-response curves to various doses of URO (given as infusion) were determined.

Results & Discussion: In our study, we found significantly higher ($p < 0\ 05$) decrease of perfusion pressure after URO administration in the group of preeclamptic placentas, compared to control placentas This effect was transient, and the period of lowering pressure has been found shorter in the preeclamptic group (statistical significance).

Conclusion: 1.) Response to urodilatin of the placental vasculature seems to be increased in preeclampsia, but this effect is temporary, **2.)** The range of placental vessels oscillations is wider in preeclamptic group

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A.518 Intrapartum fetal oxygen saturation monitoring during epidural analgesia for labour

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Background: A pulse oximeter made specifically for non-invasive, continuous intrapartum monitoring of SpO_2 has been recently introduced[1] In this preliminary open study we investigated the possible effects of uncomplicated epidural analgesia on SpO_2 during labor and delivery

Methods: Forty five healthy nulliparous parturients, at term, with uncomplicated pregnancies in established normal labor with cervical dilatation at least 2 cm requesting epidural analgesia were recruited and gave their consent for this study At least 10 min before epidural analgesia, all parturients were monitored with blood pressure, pulse oximetry, HR and FHR, uterine contractions and non-invasive fetal SpO_2 by an HP 50XM and Nellcor N-400 monitors and all these data were continuously recorded on the CTG trace until delivery. All parturients received epidural analgesia with 20 mL of 0 0625% bupivacaine with 10 μg of sufentanil, followed by a continuous infusion (10 mL/h) of bupivacaine 0 03% with sufenta 5 μg/mL

Results: The oxysensor was introduced without any problem in the majority of parturients (42/44) and minor adjustment were made to sensor placement when SpO_2 readings were not displayed on the monitor The duration of monitoring varied between 370 min to 34 min and the sensor gave adequate recordings in 74% (range 32–100%) of registration time The mean SpO_2 averaged throughout the first stage of labor was 50% (sd 10) and for each individual fetus SpO_2 values were relatively constant A transient reduction of SpO_2 was noted during uterine hypertonus due to maternal administration of oxytocin or maternal hypotension, in the presence of reactive FHR trace and normal outcome In two cases a stable reduction of SpO_2 (<20%) during end-stage decelerations was noted and associated with forceps delivery, neonatal acidosis and poor Apgar scores at delivery In three cases a cesarean section under epidural anesthesia was performed for failure to progress (n = 1) or for not reassuring FHR tracing (n = 2) and we were able to make a continuous measurement of fetal SpO_2 during the onset of epidural block and during surgery until the delivery of the baby. In these cases was noted, during the onset of epidural block, a trend toward an increase of SpO_2

Conclusions: There was no measurable effect on fetal SpO_2 following an uneventful epidural analgesia Epidural anesthesia for cesarean section may improve fetal SpO_2 Further studies on correlation between FHR changes and fetal SpO_2 during epidural anesthesia are in progress.

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A.519 A large randomized controlled trial comparing epidural bupivacaine with intramuscular pethidine for pain relief in labour in primiparous women

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Background and Goal of Study: Epidural analgesia may increase the likelihood of obstetric intervention Previous randomised studies have been small and were not analysed on an intention to treat basis [1] This randomised controlled trial examines the effect of epidural analgesia on obstetric outcome.

Methods: Following local Ethical Committee approval, written informed consent was obtained from 797 primigravidae in the later stages of uncomplicated pregnancy. Only women uncommitted to any particular form of analgesia were recruited

On admission to delivery suite in established labour, 164 women declined their randomised treatment, and 190 women required entonox only. Of the 633 women who required analgesia, 321 were randomly allocated to receive pethidine 100 mg by intramuscular injection and 312 to receive epidural bupivacaine 10–15 ml 0 25% followed by an infusion of 0 125% bupivacaine at 10 ml. Hr^{-1} with top-ups of bupivacaine 0 25% 5 ml as required. The management of labour was standardised according to the criteria for the active management of labour[2]

Pain relief scores were assessed 24 hour after delivery by the mother on a 5 point scale (excellent, good, moderate, poor, very poor). Outcomes of labour measured included the duration of the 1st and 2nd stage of labour, whether oxytocin augmentation was required and mode of delivery. Statistical analysis was performed on an intention to treat basis using Mann Whitney U test, t test and Fisher's exact test as appropriate. We also compared the groups on the basis of treatment received.

Results and Discussion: 132 women in the pethidine group (41%) required an epidural for uncontrolled pain. The intention to treat analysis showed caesarean section rates identical in both groups (12%). There no difference between the groups in other modes of delivery or syntocinon administration. When analysis was performed on the basis of treatment received, there was no significant difference in caesarean section rate but the epidural group had a significantly lower spontaneous vaginal delivery rate (56% vs. 69%, $p = 0.005$) and a longer duration of second stage ($P < 0.001$). Mothers receiving epidural analgesia rated their analgesia higher than those receiving pethidine ($P < 0.001$)

Conclusions: Our results suggest that epidural analgesia does not result in a significantly higher rate of caesarean section or instrumental delivery.

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A.520 Effect of the addition of a mini dose of clonidine to intrathecal sufentanil for labour analgesia

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Background: Intrathecal (IT) sufentanil 5–10 μg provides good analgesia. The addition 30 to 200 μg of clonidine prolonges IT sufentanil duration but increases incidence of hypotension (1, 2). Goal of study was to evaluate the analgesic efficacy and the side effects of IT sufentanil combined with 15 μg of clonidine during first stage labor.

Methods: 90 parturients, ASA 1–2, para 0–1, cervical dilatation ≤ 5 cm, were enrolled. Patients were assigned to receive through a combined spinal-epidural (CSE) needle, one of the intrathecal solution in 2 ml of saline: sufentanil 2.5 μg (S2.5); sufentanil 5 μg (S5); sufentanil 2.5 μg and Clonidine 15 μg (S2.5 C15). Duration of IT analgesia was defined as the time between IT injection and the need for epidural bupivacaine analgesia. Analgesic efficacy was assessed with a VAS was recorded before the CSE (VAS 0), at 5 min (VAS 5) and at 15 min (VAS 15) after IT injection, and the peridural injection of bupivacaine (VAS max). Total dose of bupivacaine was recorded. Hypotension was defined as a SBP < 95 cm Hg and/or a decrease >20% from baseline. Parameters recorded were: non invasive blood pressure and heart rate ephedrine requirement, motor block, respiratory rate, SpO_2, sedation, pruritus, nausea, FHR anomalies, mode of delivery. Data are expressed as mean ± DS, groups were compared with and ANOVA and Fisher'exact test. $P < 0.05$ was considered significant.

Results:

	S2.5 (n = 30)	S5 (n = 30)	S2.5 C15 (n = 30)
Analg (min)	90 ± 28*	122 ± 67	133 ± 45
VAS 0	7 ± 2	7 ± 2	7 ± 2
VAS 5	2 ± 2.3	0 ± 0.8*	1 ± 2
VAS 15	0	0	0
VAS max	5 ± 1.8	5 ± 2.1	5 ± 2
Bupi (mg)	65 ± 42	68 ± 35	54 ± 25

* $p < 0.05$ vs other groups

The incidence of hypotension (30 vs 3%) and the ephedrine requirement were increased in gr S2.5 C15. No patient had any motor block. The incidence of cesarean was doubled in group S2.5 C15 (20% vs 10%). There was no statistically significant difference among other parameters but nausea and sedation were more frequents in group S2.5 C15.

Conclusion: The association of low dose clonidine improves the analgesic efficacy of IT Sufentanil. However the incidence of hypotension is increased. Doubling IT sufentanil (2.5 to 5 μg) produced a significantly longer duration of spinal analgesia without hemodynamic effects.

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A.521 Parturient-controlled epidural analgesia: the advantages of programming volume limit per hour

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Controlling the maximum volume per hour (MVH) enables for a given bolus volume (B.PCEA) a shortening of the lock-out interval (LI) while limiting maximum volume. The aim of this study was to compare two different PCEA modes, each having identical B.PCEA and MVH, but differing LI's.

Methods and Materials: 94 parturients were selected. Only those at full term, ASA1, with cephalic presentation were included in this randomised two centre study. PCEA procedure consisted of 1) one Abbott MENAGER pump, 2) 42 ml of solution comprised of. bupi. 1.25 mg/ml sufentanil 0.75 μg/ml; epinephrine 1.25 μg/ml, 3) a 10 ml initial bolus, 4) 4 ml B.PCEA, 5) 12 ml MVH. After an effective initial analgesic bolus (EVA = 0), parturients were randomly placed into one of the two groups· group A with LI at 20 mn (n = 47), group B with LI at 10 mn and if needed, the possibility of lengthening LI to maintain appropriate MVH (n = 47). Residual pain (EVA ≥ 5) was treated with additional boluses (ADB) of bupi 0.25% or 0.375%. Analysis criteria were the ratio of the nb of B.PCEA to the nb of requests (B/D), the average nb of B.PCEA, average number of ADB, bupi. time-dose and the proportion of ADB (bupi.ad), sufentanil time-dose, EVA, satisfaction at 24 hours. The tests utilised were· Student's t-test and the chi-2.

Results: In the two groups, demographic, obstetric, neonates, analgesic procedures in time and quality as well as 24 h satisfaction were all comparable. Utilisation modes were different (table).

	Group A n = 47	Group B n = 47	p
B/D	0.74 ± 0.27	0.94 ± 0.10	<0.0001
B PCEA. nb	2.72 ± 1.85	3.53 ± 1.88	0.038
B ad. nb	0.46 ± 0.62	0.21 ± 0.41	0.021
Bupi mg/h	9.25 ± 4.28	8 ± 2.42	0.065
% Bupi.ad	18.1 ± 23.1	7 ± 13.7	0.007
Suf μg/h	4.14	4.42	0.32

Discussion and Conclusion: Given the comparable bupi consumption, identical analgesia and satisfaction, the PCEA return is better in group B since 94% of requests are satisfied. With this improved return, we are able to limit the number of ADB. MVH control may be more simply by programming decreased volume limit per hour if available on device rather than by secondary LI modifications such as in the case of our study.

A.522 Intrathecal bupivacaine reduces uterine activity in labouring and non gravid rats

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Background and Goal of Study: Loco regional analgesia can reduce uterine activity in parturient [1] and dog [2]. The aim of our study was to evaluate the effect of intrathecal (IT) 0.25% bupivacaine (BUPI) on uterine activity in labouring (G) and non gravid rats (NG)

Materials & Methods: 4 groups of 6 female Sprague-Dawley rats received IT: normal saline (Control Groups G and NG) or BUPI (groups BUPI, G and NG). Under ketamine anaesthesia and mechanical ventilation, arterial pressure (AP), intravenous (IV), IT (located between L1–L2 and L3–L4 nerve roots), and intrauterine pressure (IUP) catheters, and temperature (T) probe were implanted. After a baseline period of 20 min, 3 cumulative IT doses of BUPI (10, 10, and 20 μl) or saline were injected, followed by a recording period of 20 min. AP was maintained constant (iv starch loading). Data are mean % of baseline ± SD. Repeated-measure ANOVA was used.

Results: IUP changes are given in Figs. 1 et 2. No significant variations in AP and T were noted.

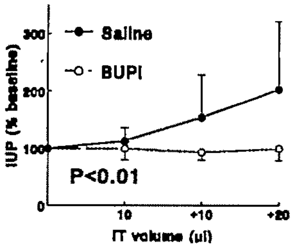

Figure 1. IUP in G rats

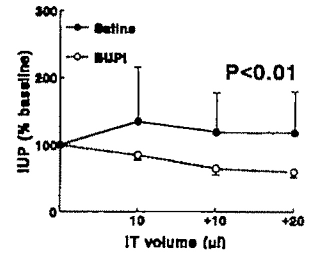

Figure 2 IUP in NG rats

Conclusion: Our results suggest that IT BUPI reduces uterine activity both in NG and G rats

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A.523 Current management of inadvertent dural taps occurring during epidural analgesia for pain relief in labour: a French postal survey

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Background and Goal of Study: According to a survey in the United Kingdom, management of dural taps occurring during epidural analgesia (EA) in labour varies widely from an institution to another (1). The different measures to manage inadvertent dural taps before and after postdural puncture headaches (PDPH) are still controversial. As the routine prophylactic and curative treatment in France is unknown, we designed a questionnaire that was sent to all french obstetric units to survey this practice.

Materials and Methods: From april to june 1997, a questionnaire including 22 items was sent to 799 french obstetric units located in both teaching and not teaching public hospitals and private institutions.

Results and Discussion: We received answers from 267 french obstetric units (response rate of 33.4%) Although management of dural taps was the same for every anesthesiologist in 52.4% of the institutions, only 8.2% had a written protocol In case of dural puncture, EA was still performed by 94.9% of the units but usually by choosing another interspace (86.8%). Large oral intake was the most frequent prophylactic measure (81.3%) To prevent PDPH, bed rest was largely ordered (76.4%) and lasted 24 hours in 46.5% of institutions. Prophylactic epidural blood patch (EBP) was performed in 13 4% of the obstetrical units. To treat PDPH, a majority of anesthesiologists performed an EBP (91 8%) and most of them respected a delay of 48 hours (62.5%). Intravenous and oral caffeine was used by 30 7% and 23.6% of the units. Prior to EBP, coagulation was assessed in about 20% of the units and blood culture in only 2.6%. 65 2% of the units stopped the injection of EBP when the patients felt backache A large range of volumes were injected but usually less than 20 mL (81 3%). 60.6% of the units discharged the patients home after an overnight stay in the hospital. If the first EBP failed, a second one was performed by 60 7%. The feeling of the anesthesiologists about performing an EBP is shown in fig. 1

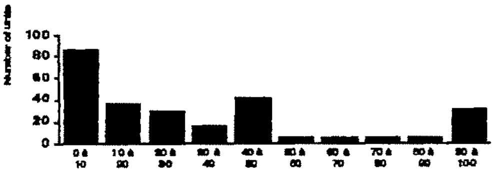

Fig 1. Distribution along analogue scale-personnel feeling about performing EBP (0 = happy/100 = unhappy) n 267

Conclusion: Management of dural taps occurring after EA for pain relief in labour differs widely from a french obstetrical unit to another Comparing with the practice in the United Kingdom (1), the main differences are: not so many protocols, no use of epidural saline infusions and larger use of caffeine

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A.524 Obstetric analgesia as a guide to progress of labour. Is it possible?

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Background & Goal of Study: Obstetricians are aware that a deep regional anaesthesia can at times interfere with the progress of labour and delivery That is why many of them still lack confidence about the real advantages of regional anaesthetic techniques It would be ideal to get a protocol that fits everyone: effective enough for the parturient, and with full agreement from the obstetrician We have developed an analgesic protocol that, being well followed by the staff and well accepted by the parturients, is also helpful for midwifes and obstetricians to know about the progress of labour.

Patients & Methods: In the last five years we have tested a combination of different local anaesthetics, concentrations, adjuvants, and perfusion rates, in order to minimally affect the progress of labour, and at the same time have a guidance about it. We selected the one that best fitted our aim, and prospectively applied it when possible.

Selected patients were those pregnant women in labour, scheduled for epidural analgesia having a cervical dilatation of 3–5 cm or in trial labour under oxytocin stimulation. After the epidural space was identified, 2 cc mepivacaine 1% was administered through the Tuohy needle The catheter was inserted and another 2 cc mepivacaine 1% administered Then a local anaesthetic perfusion was started, containing bupivacaine 0.0625% + epinephrine 1:800.000 + fentanyl 0 0002% The perfusion rate was adjusted according to the cervical dilatation (i e 4 ml/h for 4 cm cervical dilatation and so on). When the patient started to feel discomfort, a bolus of 2 cc of the perfusion solution was administered and a higher rate initiated The anaesthesiologist survey was continuous, to adapt the perfusion rate to the needs of the patients.

Results & Discussion: With the protocol described we observed that the dose of analgesia the patients needed was directly related with the cervical dilatation, in such a way that the needs of analgesia could guide the midwifes about the progression of labour. The analgesic needs were 20% higher in the cases of trial labour under oxytocin The perfusion and doses described were analgesic enough, without reducing aesthesia in lower limbs as to be unpleasant Patient satisfaction with labour assistance (pain, environment, people) was qualified as very good in more than 90% cases, what at some extent we attribute this fact to the high confidence of the patient when she feels coordination and understanding in the obstetrical-anaesthetic team. What is more, midwifes collaboration was excellent They qualified this protocol also as excellent, because they found it very useful for their practice. Since the perfusion rate was so related to the cervical dilatation, the number of gynaecological examinations was also reduced.

Conclusions: The analgesic rate of a perfusion of bupivacaine 0 0625% + epinephrine 1 800.000 + fentanyl 0.0002% to be analgesic enough is directly related to the cervical dilatation (1 ml/h per cm dilatation, plus a 20% in trial labour under oxytocin). In our hands his has proved to be a very useful guidance about labour progression

A.525 Combined spinal-epidural analgesia in labour: comparison of two doses of intrathecal bupivacaine with fentanyl

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Background and Goal of Study: Combined spinal-epidural (CSE) analgesia is an effective and popular method of labour analgesia[1] Local anaesthetic is frequently added to intrathecal opioid. However, this may cause undesired sensory and motor block, and the optimum dose is not known. We compared two doses of bupivacaine with 25 μg fentanyl

Materials and Methods: In a prospective randomized double-blind trial, 50 parturients were assigned to receive either 1.25 mg bupivacaine (Gp A) or 2.5 mg bupivacaine (Gp B), with 25 μg fentanyl, intrathecally during CSE analgesia Baseline visual analogue pain score (VAPS) was taken at the peak of a uterine contraction. After intrathecal injection, VAPS were recorded at 5-min intervals for 15 min, then every 15 min for 2 hr or until next analgesic request Sensory block, motor block, BP, HR, sedation, nausea, and pruritus were also recorded Data were analyzed using Chi-square and Mann Whitney-U tests. $p < 0\ 05$ was considered significant.

Results and Discussion: 45 patients completed the study (Group A = 21, Group B = 24). There were no differences in patient characteristics. Median VAPS of 0 was achieved by 5 min in both groups Both sensory and motor block were significantly greater in Group B. Other side effects were similar.

	Group A	Group B	p-value
Median sensory level (15 min)	T11	T6	0 002
Motor block (15 min)	Yes (n = 0) No (n = 21)	Yes (n = 6) No (n = 18)	0 0138
Median duration of analgesia (interquartile range)	75 min (75, 105)	113 min (90, 120)	0.017

Conclusions: We recommend using 1 25 mg bupivacaine intrathecally during CSE as it is as effective as 2 5 mg, with lower incidences of sensory and motor block.

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A.526 Thermoregulatory response during labour, with and without epidural analgesia

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Background: Shivering-like tremor and sweating are common during labour and delivery Their etiology, though, remains unclear One potential cause of shivering-like tremor is normal thermoregulatory shivering induced by core hypothermia or skin-surface cooling, and is preceded by peripheral vasoconstriction. On the other hand, thermoregulatory sweating occurs as a result of core hyperthermia which is preceded by vasodilation. However, both, shivering and sweating can sometimes occur in normothermic subjects as well. Non-thermoregulatory mechanisms such as pain, stress, and endocrinological responses during pregnancy might explain this phenomenon. Furthermore, shivering etiologies might differ when epidural analgesia is provided. Accordingly, we evaluated thermoregulatory response patterns during labour in delivery, with and without epidural analgesia

Methods: With IRB approval, we studied 40 consenting patients undergoing normal labour and delivery. Twenty-one patients were given epidural analgesia (bupivacaine 0.125%, 10–15 ml bolus, 0.125%, 0.1–0.2 mg/kg/h continuous infusion) The remaining group (n = 19) either had no pain medication or received a bolus dose of piritramid (0.1 mg/kg PRN).

Thermoregulatory responses were recorded at 30-minute intervals until two hours after normal delivery, or until a cesarean delivery was required. Mean core temperature was measured orally, and at the tympanic membrane. Arterio-venous shunt vasomotion was evaluated by using forearm minus fingertip skin temperature gradients Shivering and sweating were evaluated using a qualitative scale from 0 to 2 Thermal discomfort as well as pain were recorded using a 100 mm-long VAS. Data were analyzed (referring to the total number of epochs) using unpaired two-tailed t-test and $p < 0.05$ was considered significant

Results: Sweating was observed in 26% of the whole (312) epochs At 14% of the sweating epochs, patients were surprisingly hypothermic (36.3 ± 0.2°C) and vasoconstricted Shivering was observed in 23% of all epochs. Interestingly, 18% of shivering epochs was observed when the patients were normothermic (37.4 ± 0.8°C), and vasodilated At 9% of the epochs, shivering and sweating were observed at the same time in normothermic subjects (37.1 ± 0.6°C). In this group, the average pain score was found as 81 ± 20 In the epidural analgesia cases, average core temperature was found to be 0.5°C higher than the group without epidural analgesia.

Conclusion: At both, shivering and sweating epochs, the pain scores were significantly higher than the remainders. At the epochs where shivering and sweating were observed at the same time, pain seemed to be the major cause. We observed many shivering and sweating epochs which were not thermoregulatory. These extraordinary responses might be explained by pain or/and endocrinological processes occurring during labour and delivery.

INTENSIVE CARE MEDICINE

A.527 Effect of endothelin-1 on LPS clearance and bacterial killing in rabbits

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Introduction: The vasoactive peptide endothelin-1 (ET) seems to play a key role in inflammation via interaction with the release of cytokines, the generation of eicosanoids, and NO synthesis [1]. Since LPS is one potent trigger of ET-synthesis in various tissues, the aim of this study was to investigate whether ET affects host defence mechanisms such as LPS clearance and bacterial killing in rabbits.

Methods: To enable quantification of the clearance process, a defined number of viable *Escherichia (E.) coli* (10^8 CFU) were injected intravenously in anaesthetised rabbits after infusion of ET (n = 9) and in untreated controls (n = 9) respectively. Mean arterial and airway pressures were continuously monitored. To evaluate bacterial and LPS clearance, blood samples were drawn in short intervals. 180 min after bacterial injection, the animals were sacrificed and tissue samples of liver, kidney, spleen, and lung were collected for microbiological examinations.

In addition PMN, burst and phagocytic activity was determined in a flowcytometric assay to assess neutrophil microbicidal functions

Results: ET-infusion resulted in a higher MAP and airway pressure during the observation period While blood clearance of *E. coli* and LPS in ET challenged animals did not significantly differ from controls, there was an increased extrahepatic organ colonisation due to ET-infusion with fourfold higher bacterial counts in spleen and lung and a twofold increase in the kidney. PMN burst and phagocytic activities were currently evaluated

Conclusion: The increased organ colonisation after ET-infusion points towards an impaired host defence against microbial infections. Whether these effects may be related to disturbances in the microcirculatory blood flow remain to be elucidated

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A.528 Effects on platelet function of systemic inhibition of endogenous nitric oxide production by L-NMMA

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Background: Endogenous nitric oxide (NO) produced by endothelial cells has been shown to act as a continuous vasodilator of the circulatory system. *In vitro* studies have also indicated that NO produced by endothelial cells inhibit platelet function Animal studies have indicated that inhibition of NO production has prothrombotic effects and that endogenous and exogenous NO may have antithrombotic effects. Septic chock is in part mediated by increased NO production, and treatment of septic shock with N^G-monomethyl-L-arginine (L-NMMA), an inhibitor of endogenous NO, is being evaluated in clinical multicenter trails

Material and Methods: We have studied the effects of L-NMMA on platelet function *in vivo* in healthy volunteers during a 60 min infusion (n = 14) During the last 30 min concomitant inhalation of NO 30 ppm was given. The study design was randomised double-blind, placebo-controlled cross-over trial for L-NMMA (0.3 mg/kg/min for 30 min, followed by 0.15 mg/kg/min for 30 min). This dose of L-NMMA suppressed NO in nasal air by ≈65% in a previous study. Platelet function was assessed by filtragometry *ex vivo*, flow cytometry in whole blood (P-selectin expression and fibrinogen binding), measurements of platelet secretion products (β-TG) in plasma and bleeding time. In addition, thrombin generation markers (TAT, F1 + 2), and cGMP in plasma and platelets were measured.

Results: L-NMMA infusion increased systolic blood pressure by 24% ± 7% and decreased heart rate Plasma cGMP was not influenced by L-NMMA, but increased significantly during NO inhalation (from 4.00 ± 0.48 to 12.19 ± 0.86 and from 3.97 ± 0.32 to 9.23 ± 0.57 during L-NMMA and placebo, respectively, $p < 0.001$); no changes in platelet cGMP could be found. Neither platelet aggregation measured with filtragometry *ex vivo*, nor P-selectin expression or fibrinogen binding (to GPIIb-IIIa receptors) or plasma β-TG revealed significant changes, either during L-NMMA or during NO inhalation. Plasma TAT and F1 + 2 were stable. Bleeding time increased following NO inhalation ($p < 0.001$), and this effect was similar in L-NMMA and placebo experiments (24% during L-NMMA, and 28% during saline)

Conclusion: Inhibition of NO synthesis by L-NMMA had no significant effects on platelet function despite clear-cut effects on blood pressure. The addition of NO inhalation had no effects on platelet function measured with several different techniques, apart from a slight increase of bleeding time, both during L-NMMA and placebo infusions

A.529 LPS does not induce changes in hepatocellular microtubule cytoskeleton and phosphorylation of MAP-kinases

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Introduction: Lipopolysaccharides (LPS) are known to be involved in the pathogenesis of septic shock and multiorgan failure. It has been demonstrated that LPS may cause changes in monocyte cytoskeleton and directly influence assemblation of isolated microtubuli. As liver failure is increasingly observed during septic shock we estimated the influence of LPS on microtubule cytoskeleton of cultivated hepatocytes and human blood monocytes.

Methods: HepG2 cells, murine hepatocytes, or human monocytes (positive control) were incubated with LPS FITC labelled or unlabelled (0.1–200 µg/ml) up to 48 h. After staining with antibodies to tubulin and tau proteins cells were analysed by fluorescence and laser scan confocal microscopy. Activation of MAP-kinases was investigated by Western Blot using phosphospecific antibodies.

Results: Immunofluorescence revealed that the cytoskeleton of hepatocytes was not affected by LPS. Furthermore, no phosphorylation of MAP-kinases was found after LPS-incubation Mouse hepatocytes and HepG2 cells did not accumulate FITC labelled LPS. In contrast, human blood monocytes showed an accumulation of FITC-LPS, an activation of MAP-kinases and changes in microtubule cytoskeleton.

Conclusions: Our results might explain the frequently observed late onset of liver failure during sepsis-syndrom. Further studies on possible protective factors in hepatocytes and the complex co-operation between LPS and cytokines leading to hepatocellular damage are necessary.

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A.530 Human peripheral blood mononuclear cells express mRNA for procalcitonin

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Introduction: Procalcitonin (PCT), the precursor of calcitonin, is produced under physiological conditions in the thyroid It was recently identified as a marker of severe especially bacterial infection. Elevated PCT levels have been demonstrated in septic patients also after thyroidektomy Therefore other sites of PCT expression have to be considered.

Methods: Possible PCT mRNA expression in peripheral blood mononuclear cells (MNC) from healthy humans was assessed by reverse transcriptase polymerase chain reaction (RT-PCR) using a novel primer set (B R A H M S, Berlin). Levels of PCT mRNA expression were estimated in control and cultures of MNC stimulated by lipopolysaccharides (LPS) and sepsis related cytokines. Restriction mapping was performed to verify the specificity of PCR primers for human PCT by digestion of PCR amplified thyroid medullary carcinoma cDNA

Results: RT-PCR analysis demonstrated that MNC express mRNA for PCT and that LPS as well as various cytokines may modulate this expression In the cultures stimulated with LPS from E. coli B4 and Salmonella abortus equi the final RT-PCR product for PCT mRNA was elevated up to 200% to 2300% in comparison with 100% in control culture. Pronounced effects were also observed for IL-1β – 100–1800%, IL-6 – 200–3500%; TNF-α – 200–9000%; IL-2 – 250–1500%. IL-10 had no effect on the expression of mRNA for PCT.

Conclusions: We demonstrate for the first time that PCT is expressed in MNC This expression is modulated by bacterial LPS and sepsis related cytokines Therefore MNC may be one of the sources for elevated plasma PCT levels in septic patients

A.531 Effects of L-NAME on PMN-function and bacterial clearance in rabbits

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Introduction: Since the release of NO has been shown to play an important role in the vasoregulation during sepsis the use of nitric oxide synthase inhibitors was investigated in different animal models Aim of this study was to investigate, whether pretreatment with the inhibitor of nitric oxide synthase N-nitro-L-arginine-methylesther (L-NAME) affects host defense mechanisms against microbial infections. For this purpose bacterial clearance from the blood and tissues as well as PMN phagocytosis and burst activity were determined in anesthetized rabbits.

Methods: To evaluate potential effects of L-NAME on bacterial elimination and killing, blood-clearance of Escherichia (E.) coli and organ colonization were investigated in anesthetized rabbits after pretreatment with L-NAME (5 mg/kg b.w./h, n = 14) and in sham operated animals (controls, n = 14) respectively To enable quantification of the clearance process, defined numbers of exogenous E coli (10^8 CFU) were injected intravenously 60 min after the beginning of L-NAME application To characterize elimination kinetics of injected *E. coli*, blood samples were drawn for bacterial counts in short intervals Samples of liver, lung and kidney were collected 180 min following *E coli* injection, to assess organ colonization. Parameters monitored were rates of bacterial elimination from the blood, arterial pressure, blood gases and white blood cell counts 180 min after bacterial injection tissue samples of liver, kidney, spleen and lung were collected for microbiological examinations PMN phagocytosis and burst activity were determined using a flow cytometric assay Differences between groups were tested by ANOVA and subsequent multiple range test (LSD)

Microbiological Results: Compared with controls, L-NAME treatment resulted in a significantly prolonged bacterial clearance process with higher E coli concentrations in the blood ($p < 0.05$). The delayed blood-clearance was associated with significantly ($p < 0.01$) higher values of bacteria in liver, lung and kidney

Flow-cytometric Results: Pretreatment with L-NAME reduced significantly the PMN-phagocytosis ($p < 0\ 05$) but enhanced oxygen radical production

Conclusion: The impaired bacterial elimination from the blood and the enhanced organ colonisation in relation to the reduced PMN-phagocytosis point towards an impaired granulocyte dependent bacterial clearance function after pretreatment with L-NAME, thus predisposing the host to increased risk of infection.

A.532 Distribution of microcirculatory blood flow in the gastrointestinal tract during haemorrhagic shock

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Background: Hypoperfusion of splanchnic organs after hemorrhagic shock may cause severe complications such as multiple organ failure The intestinal mucosa is very vulnerable to ischemia due to a particular microvascular arrangement of the villi and high oxygen consumption of the mucosal cells that leads to low pO 2 at the villus tip even during normal blood supply. Little is known about dynamic flow-distribution within the splanchnic region in circulatory shock Recently a multichannel laser Doppler system has become available that can measure microcirculatory flow (MCBF) in multiple organs simultaneously and continuously (incl the intestinal mucosa)

Methods: Eight pigs were anesthetised and ventilated MCBF was measured in the intestinal mucosa (stomach, jejunum, colon), pancreas, liver and kidney using a six-channel laser Doppler flowmeter system Systemic hemodynamics (CI, MAP etc), superior mesenteric artery flow (SMA flow, TTF) and gastric mucosal pH (pHi, tonometry) were also measured After preparation, the animals were bled to MAP of 40 mmHg during 30 min and kept at 40 mmHg for 180 min before retransfusion of shed blood and fluids

Results: The main results are summarized in the table

Relative changes to baseline (mean ± SD)	Baseline t = 0 min	After blood loss t = 30 min	Before retransfusion t = 180 min	After retransfusion t = 210 min	After retransfusion t = 330 min
CI	100	53 ± 15	55 ± 14	99 ± 42	107 ± 32
MAP	100	43 ± 8	42 ± 8	73 ± 19	71 ± 15
SVR	100	85 ± 14	77 ± 18	78 ± 29	69 ± 19
SMA flow	100	68 ± 14	85 ± 21	153 ± 94	133 ± 37
LDF Stomach	100	65 ± 27	72 ± 28	114 ± 45	120 ± 44
LDF Jejunum	100	94 ± 15	101 ± 32	129 ± 43	115 ± 30
LDF Colon	100	84 ± 24	77 ± 29	124 ± 38	109 ± 19
LDF Pancreas	100	41 ± 14	39 ± 16	81 ± 43	80 ± 45
LDF Liver	100	71 ± 21	57 ± 36	71 ± 26	82 ± 36
LDF Kidney	100	70 ± 20	63 ± 25	124 ± 99	141 ± 98
pHI	7 23 ± 0 06	7 20 ± 0 08	7 13 ± 0 07	7 17 ± 0 04	7 19 ± 0 07

Discussion: During shock, mucosal flow in the stomach and colon decreased by 15–30%, similar to the SMA flow, while the jejunal flow remained virtually unchanged Flow in the liver and kidney decreased somewhat more (30–40%), but flow in the pancreas was most severely affected (decreased by 60%) After retransfusion of shed blood SMA flow increased by 30–50% and mucosal flow (stomach, jejunum, colon) by 10–30% as compared with baseline Although microcirculatory flow in the pancreas and liver increased slightly after retransfusion it remained significantly depressed (20–30% below baseline)

Conclusion: During hemorrhagic shock and after fluid volume resuscitation there was a considerable difference in microcirculatory flow changes in the various parts of the gastrointestinal tract studied The jejunal mucosa was the least severely affected (remained unchanged) while the pancreas was most the most severely affected organ studied with 60% decrease in microcirculatory flow during shock.

A.533 Tissue hypoxanthine reflects splanchnic vulnerability in porcine endotoxin shock

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Background & Goal of Study: The splanchnic region has been reported as specifically vulnerable during shock states[1–3]. In this study we evaluated potential interorgan differences in interstitial hypoxanthine, a metabolite of ATP degradation and cellular energy failure, during progressive endotoxin shock in the pig.

Materials & Methods: Seventeen pigs were anaesthetised and catheterised. Tissue levels of hypoxanthine, assessed by in vivo microdialysis (human probe 30 mm, CMA, Sweden), were monitored in several organs (ileum, liver, lung, skeletal muscle, subcutaneous fat and arterial blood) simultaneously in addition to central hemodynamics. Ten pigs were subject to endotoxemia (20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) while seven sham animals served as controls The experiments were terminated 5 h after onset of endotoxemia

Results & Discussion: Tissue hypoxanthine and hemodynamics proved to be stable in the sham group while marked changes were seen in central hemodynamic parameters in response to endotoxemia. The most prominent increase in hypoxanthine was seen in the ileum (277% of baseline at 5 h) while only limited changes were observed in skeletal muscle and fat Intermediate increases were seen in the liver, lung and arterial blood. These results indicate a differentiated development of ATP degradation and cellular energy failure in response to endotoxemia in different organs Considering the high amounts of xanthine oxidase seen in the gut the increases in hypoxanthine may provide an important substrate for reactive oxygen species formation in these organs. Furthermore, these results suggest that microdialysis in subcutaneous fat commonly used in the clinical setting may prove to be of limited sensitivity during septic conditions

Conclusion: These findings support previous reports of specific vulnerability of the splanchnic organs during endotoxemia.

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A.534 Mitochondrial redox state in septic shock

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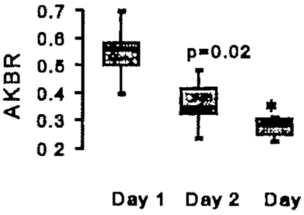
Background and Goal of Study: Patho-physiological changes occurring as a result of severe infection may poison normal intracellular metabolic processes. There is much interest in measurement of arterial ketone body ratio (AKBR), the ratio of acetoacetate to 3-hydroxybutyrate in patients with sepsis as a marker of mitochondrial redox state Aim is to investigate AKBR and plasma lactate in critically ill patients with and without septic shock, and to assess their usefulness as indices of clinical status.

Materials and Methods: Patients were enrolled into the study following Ethics Committee approval and patient consent. Ten patients fulfilled the Consensus Conference Criteria for sepsis. Ten non-infected APACHE II matched control patients were also studied. Blood samples were taken after an intravenous bolus administration of 15 g glucose (to suppress ketogenesis). Sampling was repeated at 24 and 48 hrs. AKBR was measured using the Ketorex C Kit (Genzyme Diagnostics). Data expressed as median and range and compared by using Mann Whitney U test or Kruskal-Wallis analysis of variance.

Results: Six (60%) patients died in the septic group and 3 patients (30%) died in the control group. AKBR decreased over the 3 days in the septic patients who died ($p = 0.002$, Figure) and AKBR was lower on day 3 in these patients compared to survivors ($p = 0.019$). AKBR in non-septic controls did not change and was not different from septic patients. However, AKBR in all patients was lower on day 3 in those who died than in survivors ($p = 0.002$).whether septic or non-septic Lactate did not change over the 3 days in any group, but the lactate concentrations were higher in non-survivors on day 3 than in survivors, in septic ($p= 0.01$), non-septic ($p = 0.017$) and all patients ($p = 0.002$). Lactate correlated negatively with AKBR on day 3 ($r = -0\ 53$, $p = 0\ 015$)



Conclusion: Decreased AKBR and increased lactate concentration were associated with non-survival in critically ill patients, especially with sepsis: Serial AKBR could be useful to assess effectiveness of therapeutic interventions

A.535 Role of the liver in interleukin-10 production in a porcine model of endotoxicosis

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Background and Goal of Study: Sepsis induces the release of several endotoxins, including proinflammatory and anti-inflammatory mediators. An uncontrolled inflammatory response has been implicated as an important pathogenic component of multiple systemic organ failure (1). It has been observed that interleukine-10 (IL-10), an anti-inflammatory cytokine, prevents lethality in experimental endotoxemia (2). The endogenous release of this cytokine could be produced in the early stage of sepsis and contribute to the control of proinflammatory mediators release such as TNF and IFN-γ, hence exerting a protective effect. It has been suggested that the liver itself could be a major source of IL-10 in Orthotopic Transplantation (3) The aim of the present study was to evaluate the particular role of the liver in IL-10 secretion in a porcine model of septic shock.

Materials and Methods: Pigs were injected with 1 to 50 μg of liposaccharide (LPS) via the portal vein (PV) ($n = 5$) or the pulmonary artery (PA) ($n = 6$), under general anesthesia Control animals ($n = 4$) were injected with saline in the same conditions Systemic and pulmonary blood pressure, cardiac output and oxygen extraction were continuously monitored during the experience. Serum levels of TNF and IL-10 were measured on blood samples from PV, suprahepatic vein, PA and femoral artery at different times after LPS injection. Cytokines levels were compared by student T-tests. $p < 0.05$ was accepted as significant

Results: In all experimental conditions, independently from the site of injection, the administration of LPS induced a profound state of septic shock indicated by systemic hypotension, tachycardia, decreased cardiac output and progressive acidosis This was correlated with TNF secretion (mean ± SE. 280 ± 281 U/ml at the peak, 60 min after LPS injection). In the 11 pigs injected with various amounts of LPS, in a dose-dependent manner, we detected a significant release of IL-10 (mean ± SE 450 ± 278 U/ml at the peak, 45 min after LPS injection) ($p < 0.05$ control vs LPS group). IL-10 was not measurable at any time in control pigs, injected with saline. There was no statistical differences in cytokines production between PV or PA LPS site of injection. Finally, we found no significant differences in IL-10 concentrations between portal vein, suprahepatic vein, pulmonary artery and femoral artery.

Conclusions: Septic shock, induced by the injection of LPS in pigs, is associated with a rapid and massive release of IL-10. The liver is not a predominant site of production of this cytokine in this situation

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A.536 Prognostic value of immunomonitoring in patients with polytrauma and sepsis

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Background and Goal of Study: Thrombomodulin (TM) and procalcitonin (PCT) are released as a result of endothelial damage and systemic inflammation, respectively In addition, the expression of HLA-DR (%HLA-DR), and the ratio of T-helper to T-suppressor cells (CD4/CD8) on peripheral blood mononuclear cells (PBMC) are important markers of the corresponding cellular immune response. In this study, the prognostic value of TM, PCT, CD4/CD8 and %HLA-DR in patients after polytrauma and sepsis was investigated

Materials and Methods: 65 intensive care patients with polytrauma (P) and sepsis (S) were studied on day 1, 2, 3, 7, 10 and 14. TM and PCT were measured in plasma using ELISA (Diagnostica Stago) and ILMA (B.R.A H.M S.), respectively HLA-DR expression and CD4/CD8 were determined on PBMC by flow cytometry. We analyzed the relation between these soluble and cellular markers and the survival in group P and S

Results and Discussion: TM plasma concentrations (ng/ml) were significantly higher in septic patients than in patients after polytrauma (91 ± 45 vs. 40 ± 7 on d3). Polytrauma survivors and non-survivors can be discriminated by TM (60 vs. 31 ng/ml, mean d1–3) within the first three days. PCT plasma levels always decreased during the first days after polytrauma regardless of the outcome, but increased again in non-survivors. In group S, PCT was significantly increased and returned back to normal in survivors, but remained elevated above normal in non-survivors. Mean %HLA-DR positive blood monocytes was significantly reduced until day 10 both in group P and S compared with normal subjects. Whereas %HLA-DR was significantly lower on day 10 and 14 in septic patients who died, %HLA-DR could not discriminate survivors and non-survivors in polytrauma patients. In group S, non-survivors also showed diminished CD4/CD8 ratios that were consistently lower than in survivors, whereas in group P, CD4/CD8 was always increased and independent of the outcome.

Conclusion: TM may serve as a marker for injury severity in polytrauma patients discriminating survivors and non-survivors. The course of PCT seems to correlate with the outcome after polytrauma and sepsis. HLA-DR expression on monocytes and CD4/CD8 ratio are valuable prognostic markers in septic, but not in polytrauma patients.

A.537 Lactic acidosis during fulminant hepatic failure: determinants and infectious complications

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Background and Goal of Study: In patients with fulminant hepatic failure (FHF), regional oxygen uptake becomes inadequate for tissue requenments The presence of lactic acidosis is a common feature which suggests tissue hypoxia. It contributes to bacterial translocation and sepsis leading to multiple organ failure which has a poor prognosis The aim of the study is to identify the hemodynamic and oxygenation parameters as well as the degree of encephalopathy and the incidence of infectious complications that may correlate with lactic acidosis in patients with FHF submitted to liver transplantation

Patients and Methods: Fifty-four patients with FHF (failure group (FG)) and 100 patients with end stage liver disease (control group CG) were studied Variables analyzed were age, mean arterial blood pressure, cardiac index, systemic vascular resistance, portal pressure gradient, arteriovenous oxygen difference, oxygen consumption, oxygen extraction ratio, respiratory quotient, plasma lactate levels, intrapulmonary shunt, degree of encephalopathy, intracranial pressure and infectious complications Statistical analysis was performed by means of *t* test and regression analysis. Data are reported as mean ± SE

Results: Both groups differed only in the degree of portal hypertension (FG: 12 5 ± 1 *vs* CG: 20 ± 0.7 mmHg, $p < 0\ 001$), and encephalopathy (FG. 3.8 ± 0 2 *vs* CG. 1 2 ± 0 05, $p < 0.001$) Moreover, 14/54 patients (51%) with FHF versus 13/100 (13%) presented any infectious process ($p = 0.04$) Among variables analyzed, only respiratory quotient was significantly related to the level of lactic acidosis.

Conclusions: 1) Both, hyperdynamic state and the degree of encephalopathy during FHF did not correlate with lactic acidosis. 2) There was no association between the degree of lactic acidosis and the incidence of infection 3) Finally, our data suggest an association between FHF and infectious complications.

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A.538 Influence of n-acetylcysteine on leucocyte functions in critically ill patients

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Introduction: The antioxidant N-Acetylcysteine (NAC) has been shown to attenuate septic tissue injury [1, 2]. To evaluate whether NAC affects host defence mechanisms in critically ill patients, thus predisposing to increased risk of infection, the current study focuses on neutrophil phagocytotic and burst activity after treatment with NAC.

Patients and Methods: Until now, 26 patients diagnosed with sepsis/SIRS, pancreatitis or multiple trauma from the operative intensive care unit were included. All of them were mechanically ventilated when enrolled in the study 14 patients were treated with NAC in increasing doses (Table) for four days Blood samples were taken prior to NAC infusion (day 1), after increasing doses of NAC (day 3 and 5) and four days after the last treatment (day 8)

NAC (g/24 h)	6	12	18	18	–	–
day	1	2	3	4	5	8
PMN function	x	–	x	–	x	x

The same protocol was performed in 12 patients with comparable diseases which did not get NAC (controls). Neutrophil oxidative burst activity after stimulation with *Escherichia coli* and phorbol 12-myristat 13-actate (PMA) as well as PMN phagocytosis were determined in a flow cytometric assay. Differences between groups were tested by Student's t-test.

Results: Baseline values of PMN functions were comparable in both groups NAC treatment resulted in a significantly improved phagocytosis activity after increasing NAC up to 18g per day ($p < 0.05$, day 5) compared to control patients (mean values ± SEM: 398.2 ± 99.5 vs. 65 ± 8 4). In contrast to this, PMN burst activity did not differ significantly in NAC treated and control patients during the observation period.

Conclusion: These findings suggest that infusion of NAC in high doses did not impair granulocyte function in critically ill patients The enhanced phagocytotic activity point towards an improved granulocyte dependent host defence which may reduce the risk of infection

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A.539 Plasma purification in treatment of patients with destructive forms of pancreatitis

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Goal: study of the efficiency of plasma purification during complex treatment of the patients with destructive forms of pancreatitis.

Stage of the intoxication was defined following clinical picture, presence of circulatory disorders, and three tests as well leucosytic index of intoxication, middle molecules mass in plasma and erythrocytes, circulating immune complexes Following it three groups of endotoxins were subtracted:

1st group 1.5 middle molecules fraction 0 25–0 5

2nd group 4–8 middle molecules fraction 0 5–1

3rd group 9–11 middle molecules fraction >1

Every patient underwent plasma purification by PF-05 apparatus, in constant regimen, involving venous extracorporal circle, using subclavian and femoral veins, volume of plasma exfusion was 70–80%

The efficiency of plasma purification was judged by such features as clinical and biochemical blood analysis.

Usage of plasma purification during complex treatment of the patients with destructive forms of pancreatitis gives the possibility to reach marked clinical effects and to improve the value of immunological status thus reducing the period of treatment of the patients in the intensive therapy department and to reduce mortality rate

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A.540 Procalcitonin and systemic inflammatory response syndrome in postoperative intensive care patients

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Background and Goal of the Study: Recent studies provide evidence that procalcitonin (PCT) is a reliable parameter for the evaluation of the activity and severity of infectious diseases in critically ill patients (1, 2) The present study was performed to investigate if the determination of serum procalcitonin concentrations can be useful in order to differentiate the state of systemic inflammatory response syndrome (SIRS) in postoperative intensive care patients.

Materials and Methods: 44 patients, 36 of whom met at least two of the criteria of SIRS [3], were studied With regard to the origin and course of the systemic inflammatory process the patients could be allocated to four groups: patients without apparent SIRS (I, control), patients suffering from SIRS without infection (II), without microbiologically proven infection but with successful anticipated antibiotic treatment (III), with microbiologically documented infection and confirmed or adjusted antibiotic treatment (IV). Mean values were calculated considering the daily determined serum PCT concentrations of day 1 to 5, and the maximal PCT levels of the intervals day 6 to 9 and day 10 until patients' discharge, respectively Within-group statistical analysis was performed using a Friedman-test followed by a Wilcoxon-Wilcox test, between-group statistics was calculated using a Kruskal-Wallis-test followed by a Durr-test

Results and Discussion: Serum PCT concentrations in group II remained almost within normal range and did not differ from the values obtained in the control group By contrast the PCT levels in group III and IV were markedly, and in part significantly, elevated compared to the control group These findings indicate that, in case of systemic inflammatory response, serum PCT concentrations are related to the presence or absence of microbial infection In addition, serum PCT concentrations in group III and IV decreased significantly under successful antibiotic treatment, suggesting that serum PCT concentrations reflect the state of severity of infection

Conclusions: Serum PCT concentration seems to be a suitable parameter to assess systemic inflammatory response in postoperative intensive care patients In addition, PCT may be helpful in surveying the efficacy of antibiotic treatment during the course of microbial infection

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A.541 Criteria of severity and prognosis of severe asthma and status asthmaticus: a new approach to diagnosis

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Background & Goal of Study: Effective and objective assessment of patient state's severity degree (PSSD) in Status Asthmaticus (SA) is a matter of topical interest in intensive care (IC). To raise efficacy of IC of SA through accelerating diagnosis and prognosis of SA outcome we used mathematical modelling.

Materials & Methods: Mathematical models of SA had been worked out on the base of statistical analysis computing data massif from 130 indices of 230 patients with severe asthma in SA Correlation analysis, the A. Ivakhnenkos' arguments group registration method had been used.

Results & Discussion: Mathematical models of SA have a form of the regression equations Here we present one version Y = −1.114 + 0 092X1 + 0.147X2 + 0 009X3 + 0 195X4 + 0.046X5 + 0 078X6 + 0 087X7+ 0.043X8 + 0.057X9 + 0.002X10 + 0.0095X11 + 0.214X18 + 0.134X27 + 0.372X37 + 0.001X44, where Y = index of PSSD, X1 = lucidity of consciousness; X2 = activity (position in bed); X3 = number of respiration per min., X4 = character of respiration; X5 = state of skin; X6 = cyanosis degree, X7 & X8 = lung auscultation data; X9 = sputum drainage; X10 = pulse rate; X14 = leucocytonic intoxication index; X16 = capillary blood PaCO2; X18 = lactic acid blood concentration; X27 = activity of blood AsAT, X37 = concentration of blood medial molecular peptides, X44 = concentration of circulating immune complexes. The meanings of $Y < 1.5$ conforms to the prolonged asthmatic attack; $1\ 5 < Y < 2.5$ conforms to I–II stages of SA, Y more than 2 5 conforms to III stage of SA The meanings of Y more than 3 5 with a tendency to rising were considered as unfavourable prognostication sign The trustworthiness of mathematical models' prognosis is 85%

Conclusion: Applying of mathematical modelling techniques led to reduction of the diagnosis time by a factor of 3; to ensuring the diagnosis reliability no less than 85%. It gives an efficient choice of optimum of IC and timely application of "active" methods· hemapheresis, hemoperfusion, hemo- or plasmoxenosplenoperfusion through pig spleen, ultraviolet irradiation of autoblood It allowed to reduce SA cupping time by a factor of 2.

A.542 Severe asthma and status asthmaticus: a role of xenosplenoperfusion in intensive care based on SIRS conception

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Background & Goal of Study: It is not obvious, but the main mechanisms of pathogenesis of severe bronchial asthma (BA) and status asthmaticus (SA) is nonspecific systemic response (to allergens, infection, etc) with endogenous intoxication which intensified blockade of beta-2-adrenoreceptors. The goal of study was to prove on base of Systemic Inflammatory Response Syndrome (SIRS) conception that intensive care (IC) of severe BA and SA demands application of methods of active mediatoric management (MAMM) as obligatory component.

Materials & Methods: Analysis of treatment of 90 cases with severe BA (70 – in SA, stage I–II; 20 – in hypoxic & hypercapnic coma) had been done. Routine IC had been applied in 68 cases, IC with MAMM – in 22 ones. Protocol of treatment with active mediatoric management included fractional plasmapheresis with subsequent xenosplenoperfusion of obtained plasma through pig spleen, plasmatransfusion or hemoxenosplenoperfusion (original technique reserved: 29 12 87 SU 1556680; 24.07.97 UA 24223).

Results & Discussion: It had been considered that SA is a critical state with MOSF Simultaneous lesion of 4 organs had been revealed in 65 cases; 3 organs – in 78 ones. Respiratory insufficiency (artificial lung ventilation were carried out in 12 cases), incompetence of systemic and pulmonary circulation, endogenous intoxication due to severe metabolic, immunologic disorders and disbalance of cytokines confirmed SIRS presence It had been considered that complex IC with MAMM secured 30–50% reduction of SA cupping time and 40–50% reduction of treatment term in ICU, prolonged remission to 6–14 months. The lethality level had been decreased by a factor of 1.5–2

Conclusion: Complex IC of severe BA and SA with MOSF by application of active mediatoric management methods (plasma-or hemoxenosplenoperfusion) secured improvement of treatment results due to active detoxication, immunocorrection; restoration of patient's natural mechanisms of anti-infectious defence and systemic ability to detoxication

A.543 Tip-Hub story. Our experience

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Background and Goal of Study: This prospective study was designed to analyze colonization of different parts of Central Venous Catheters and their relation to catheter-connected infections.

Materials and Methods: 84 PVC single lumen catheters for routine IV therapy and alimentary support of surgical ICU patients were included in the study After removal, 5 cm peace of the distal segment including the catheter tip was sectioned and sent to microbiology laboratory in sterile tube. The same was done with the catheter hub. Microbiological culture was done with Brun-Buison[1] modification of Cleri's[2] quantitative dilution technique. Findings were compared with the patient's clinical status x^2-test was employed for non-parametric data analysis.

Results and Discussion: Of 84 catheters, there were 27 positive tip cultures and 38 positive hub cultures Twenty one of 27 positive tip cultures were also positive hub cultures. This population of 21 was further analyzed by tipisation of the microorganisms. Tipisation revealed that in 15 cases catheter tip was colonized with the same flora as the hub, which suggests the hub as portal of entry ($x^2 = 3.85$). Join tip-hub colonization was connected with the highest incidence of catheter related sepsis and with the highest number of organisms recovered from quantitative culture ($5 \times 10^3 - 10^4$ CFU/ml).

Conclusion: The results of this study suggest that catheter hub colonization is an important step in pathogenesis of catheter related sepsis in our population of patients

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A.544 Incidence of infection of arterial catheters in intensive care patients

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Background and Goal of the Study: First, the indications of invasive monitoring of arterial pressure with an indwelling catheter and its site of insertion in intensive care patients remain controversial Secondly, in comparison with studies dedicated to central venous catheters, there is little information about arterial catheter related sepsis (ART-CRS). That is the reason why we have initiated a prospective survey of ART-CRS in our polyvalent intensive care unit without modifying our existing practice

Methods: Thanks a catheter report form enclosed in each medical patient file, the following variables have been prospectively collected· **1) after the insertion of the catheter:** patient clinical data (underlying disease, SAPS II, ...), insertion site (radial, femoral, or humeral), number of punctures, operator's level of training, and insertion context (emergency or scheduled), **2) events during the use of the catheter:** antibiotic therapy, shock, **3) after the removal of the catheter:** reason for removal (suspicion of ART-CRS, mechanical problems [complete or partial obstruction leading to not reliable arterial pressure monitoring, inadvertent withdrawal], no more indicating, death), inflammation around of the exit-site just before the removal, and duration of catheterization.

A quantitative culture of the tip of the intravascular device according to *Brun-buisson et al* was performed. The diagnosis of catheter-related sepsis was based on clinical and microbiologic criteria[1].

Results: Between November 1996 and July 1997, 108 patients (age 67 ± 16 years), 141 catheters, and 1368 catheter-days were analysed. The following table shows the microbiologic results according to the insertion site.

	Total	(+)	$>10^3$	ILC	Duration (d)
Radial	108	31 29%	20 19%	4 4%	8 8 ± 7.3
Femoral	21	10 48%	7 33%	1 5%	9 1 ± 5 8
Humeral	12	7 58%	5 42%	2 17%	19 8 ± 9 7

Conclusion: A prospective survey of ART-CRS in intensive care patients permitted us to show prolonged catheterization durations (mainly for humeral catheters, probably because of difficult arterial access of the concerned patients) associated with high colonization and infection rates.

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A.545 An intravenous catheter does not influence cytokine plasma concentrations

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Background: Plasma levels of several substances are used as prognostic or biological markers and as a tool to study patho-physiological pathways. However, preanalytical variance can disturb the measurement accuracy. We studied the effect of the presence of an intravenous catheter in human volunteers on measurements of several biological substances in plasma.

Materials and Methods: In this cross-over randomized study, at 8 a m twelve volunteers received no catheter or a catheter in the antecubital vein after initial bloodsampling. At 3 p.m. another blood sample from the contralateral vein was withdrawn.

Results and Discussion: Good correlations and no significant differences between samples were found for gp 130, IL-6, IL-6R, LIFR, CRP, IL-1RA, sCD8, sCD25 Cortisol and CC 16 (Clara Cell Protein) levels were significantly lower at 3 p.m. both with and without catheter

Conclusion: for all measured cytokines, no influence of the presence of intravenous catheters was found. Circadian variations for cortisol and CC16 were observed.

A.546 Central venous catheterization in leukaemic patients with bleeding risk

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Background: We report our experience in positioning tunnelized central venous catheters in patients affected by hematological malignancies with bleeding disorders. Correction of bleeding disorders with Fresh Frozen Plasma and/or platelets infusion may decrease the incidence of related complications, but the administration of blood products is no risk-free and often it is impossible administer blood products prior to obtaining central venous access

Materials: We enrolled 68 consecutive patients (38 M/30 F) (median age. 34 yrs) with the following PLT counts PLT > 30.000 < 50 000/mL: 16 pts, PLT > 10.000 < 30 000/mL 32 pts, PLT < 10 000/mL 20 pts. In all patients PTT and PT was lower than 1 2 the normal values for the laboratory The catheters placed included Groshong 7F (60 pts) and 12 F dialysis catheter (8 pts) No patients received PLT infusion prior to the procedure.

Results: The subclavian vein was cannulated in 52 pts, the internal jugular vein in 16 pts. Fifty-four catheters (80%) were placed with a single pass of the needle, eight catheter placement (11%) required 3 or more (maximum 6) attempts. No serious complications were recorded (pnx, hemothorax, hemomediastinum, arterial puncture, etc) Five patients (7.3%) developed bleeding at the catheter exit site and seven (10 3%) had bleeding related to skin suture treated with local pressure and ice-bag

Conclusions: In our experience serious bleeding problems related to central venous cannulation is rare. Minor bleeding problems are easily controlled by local pressure and ice-bag The risk of bleeding complications seem to be independent to the approach used (1, 2) Correction of bleeding disorders by infusion of FFP and PLT is often done prior CVC insertion to minimize the bleeding risk but to our knowledge there are no report confirming this assumption. We conclude that CVC insertion can be safely performed by experienced physicians in patients with low thrombocyte count even without PLT infusion prior to the procedure

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A.547 Significance of *Candida* species growth in respiratory samples from non-neutropenic patients in a surgical ICU

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Background and Goal of Study: Critically ill surgical patients mechanically ventilated and treated with broad spectrum antibiotics are at risk of fungal colonization[1]. The threshold for infection and the indication for antifungal treatment are a dilemma

Materials and Methods: 656 patients admitted for more than 48 hours in a 8 bed Surgical Intensive Care Unit (SICU), from January 95 to October 97, were retrospectively analysed for the presence of *Candida* in respiratory samples taken from patients with respiratory tract infection.

Results and Discussion: 69 of the 656 patients (10.5%) had *Candida* growths in respiratory quantitative cultures Groups A = 11 patients with clinical pneumonia (VAP) whose *Candida* was the only isolated microorganism, B = 25 patients with VAP and polymicrobial culture; C = 8 patients with purulent tracheobronquitis (PTB) where only *Candida* was isolated and D = 25 patients suffering PTB with *Candida* and other isolated microorganisms 58% of the patients received antifungal therapy

Patients group	Apache II	Infection day	M v days	SICU length
VAP *Candida*	21 5 (7 7)	5 7 (2 4)	14 4 (7 4)	19 8 (14)
VAP Polymic	20 2 (5 7)	8 6 (7 3)	16 8 (13)	21 (13 4)
PTB *Candida*	22 5 (6 1)	5 5 (4 2)	11 7 (6 7)	17 (10)
PTB Polymic	18 4 (7 5)	6 7 (5 6)	14 5 (10)	17 (10 2)

M v = mechanical ventilation Data mean (SD)

We have not found statistically significant differences between the four studied groups. Only 1 patient developed invasive candidemia with a fatal outcome (1/69:1.4%) 2 patients (2/69·2.9%) had positive blood cultures. Crude mortality was 33.3% (23/69). None of the patients with PTB died due to infection.

Conclusion: *Candida* isolation in respiratory samples does not seem to imply a severe infection, hence suggesting a colonization

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Candida spp

A.548 Community acquired pneumonia of rare origin

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Community acquired pneumonia (CAP) is usually an uncomplicated case However, sometimes intensive care and even mechanical ventilation and circulatory support can be necessary if complicated with severe cardiorespiratory insufficiency (According to the literature in these cases the mortality of the mechanically ventilated patients can reach the 65–100%!)

Between 1995 and 1997 24 patients were admitted to our department with the diagnosis of CAP because of severe cardiorespiratory insufficiency Mean age was 29 years, 13 female and 11 male BAL, serology and the other conventional technics were used for establishing diagnosis The invective agents were· Mycoplasma in 10 cases, Legionella in 5 cases, Clamydia in 2 cases, virus in 2 cases and fungi in 3 cases We could not identify the invective agent in 2 cases

11 patients needed mechanical ventilation, the mean time on the ventilator was 26 days Mechanical ventilation could be avoided for 13 patients using the combination of the drug therapy and the aggressive physiotherapy (drug inhalation, NIPPV and Directed Forced Inspiratory Breathing) Severe clinical status was typical for all the 24 cases, but there was a correlation between the clinical presentation and the chest X-ray only in 6 cases (25%) When the chest X-ray morphology and clinical presentation suggested atypical agent, the usual empirical (combined) antibiotic therapy were supplemented with macrolid agent Targeted antibiotic therapy was started after the results of the resistance All the patients with septic shock (10 patients of all) were mechanically ventilated and 100% of them needed the combined inotropic therapy (dopamine + dobutamine + norepinephrine or/and epinephrin) and large dose volume substitution Among those who required artificial ventilation (11), 3 patients had died (27%).

We concluded, that the community acquired pneumonia caused by atypical agents often occur in healthy young adults with severe cardiorespiratory insufficiency The mycoplasma infection considered mild in nature so far, seems to be more dangerous. The complex intensive therapy and aggressive physiotherapy could be the lifesaving cornerstones of the treatment

A.549 Early postoperative percutaneous dilatational tracheotomy after cardiac surgery

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Methods: From 11/95 until 4/97 45 (1.6%) percutaneous dilatational tracheostomies were performed in a nonselected patient series of 2788 open cardiac surgery cases

Results: Tracheotomy was performed as early as postop, day (mean 6, range 2–14), when extubation was not foreseen within the next few days Duration of intubation was 13 days (mean) In five patients we observed 6 complications (13 3%), including, bleeding, misplacement of the tube, subcutaneous emphysema and superficial infection of the tracheostoma Mediastinitis and wound infection of the sternal wound did not occur in a single case Overall mortality was 26 7% No death occurred because of tracheotomy. Underlying disease was reason for the mortality Clinically evident tracheal stenosis and inadequate granulation of the stoma were nor seen after extubation.

Conclusions: Percutaneous dilatational tracheotomy is feasible with good results and minimal risk early after cardiac surgery with midline sternotomy. Increasing incidence of mediastinitis or infection of the sternal wound was not seen In our opinion, percutaneous dilatational tracheostomy is superior to standard surgical tracheotomy early after cardiac surgery

A.550 Early extubation after cardiac surgery: safe postoperative care management

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Background and Goal of Study: "Fast track" concept, which includes early extubation and early discharge from ICU [1,2], is a new trend to manage patients after cardiac surgery (CS). The goal of the study was to evaluate whether rapid emergence from anaesthesia along with earlier extubation would provide stable postoperative haemodynamics and good balance between oxygen delivery and oxygen consumption (DO_2/VO_2) after CS

Patients and Methods: We studied 20 cardiac patients, 59 (±11) years old undergoing elective CS. All patients were anesthetized with balanced technique with moderate doses of fentanyl. Anesthesia was maintained with isofluorane before bypass and with propofol infusion during and after bypass We measured mean blood pressure (MBP), mean pulmonary artery pressure (mPAP), continuous mixed venous saturation (cSvO2) and cardiac output. Cardiac index (CI), systemic and pulmonary vascular resistances (SVR, PVR) and quotient DO_2/VO_2 were calculated by standard formulae. All parameters were measured at post-anaesthesic induction (T1), after-bypass (T2), 20 minutes after initiation spontaneous ventilation (T3) and at extubation (T4).

Results: Results are shown in table 1. Time from the end of surgery to extubation was 330 ± 65 minutes

Table 1

	T1	T2	T3	T4
MBP (mmHg)	76 ± 11	78 ± 10	83 ± 14	79 ± 9
mPAP (mmHg)	20 ± 5	20 ± 5	20 ± 4	19 ± 4
CI (L/min/m^2)	1 8* ± 0 4	3 1* ± 0.9	3 3 ± 0 5	3.5 ± 0 5
PVR (mmHg)	167* ± 84	125* ± 47	138 ± 45	139 ± 63
SVR (mmHg)	1717* ± 480	1036* ± 230	1034 ± 293	1040 ± 346
SvO_2 (%)	76 ± 7	80 ± 6	76 ± 7	76 ± 7
DO_2/VO_2 (%)	0 25* ± 0 7	0 26* ± 0.7	0 22 ± 0.7	0 21 ± 0.6

Values expressed as Mean ± SD. *p < 0 05 T1 *vs* T2 (T-Test).

Conclusions: Fast track of patients undergoing CS does not result in haemodynamic instability nor in an imbalance between DO_2/VO_2

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A.551 Lung injury score after cardiac surgery with CPB

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Background & Goal of Study: It is well known since long time ago, that cardiopulmonary bypass (CPB) alters pulmonary function, inducing a spectrum of lung pathology similar to that of acute lung injury[1] The aim of this study is to report prospectively the evolution of the Lung Injury Score (LIS)[2], as a mean to evaluate the degree of this acute lung injury after cardiac surgery with CPB.

Material & Methods: Patients admitted to the surgical intensive care unit (SICU) after scheduled cardiac surgery were included. Obstructive chronical pulmonary disease was an exclusion criteria The score was obtained at admission in the SICU, at intervals of six hours the first 24 hours and at the 2nd and 3rd day. Type of surgery, length of CPB and cross-clamping and length of mechanical ventilation were recorded. Data are presented as mean values; for LIS scores, 95% confidence interval is given between brackets Statistical analysis was made with the Student's t and ANOVA tests, considering $p \leq 0.05$ as significance level.

Results & Discussion: Fifty patients were studied, age 60.2 years, 31 men (62%) and 19 women (38%). CABG was performed in 29 (58%). Time of CPB and cross-clamping were 111.6 and 72 9 minutes respectively. Extubation could be performed before 24 hours (10 5 hours) in 88% and in the remaining 12% after (49.1 hours) Scores in LIS were: admission, 0 2 (0.03–0.37); 6 hours, 0.15 (0 03–0.33), 12 hours, 0.4 (0 2–0.6); 18 hours, 0.58 (0.38–0.77); 24 hours, 0 46 (0.26–0 66); 48 hours, 0 45 (0.25–0 66) and 72 hours, 0.47 (0.23–0.7). This increase in LIS score from 18 hours and on, was significant ($p < 0\ 0009$). There were not differences between CABG and valve surgery ($p < 0.11$). Patients with CPB lengthening more than 90 minutes did not have higher scores ($p < 0.1$). Patients with mechanical ventilation ≥ 24 hours had a maximal score of 1 14, and patients with <24 hours a score of 0.74 ($p < 0.025$). General anaesthesia, midesternal incision, extravascular lung water, CPB and other factors are responsible for increase in LIS after cardiac surgery[3]. An elevated work of breathing after extubation is reflexed by a new increase in LIS from 18 hours postadmission.

Conclusion: Evolution of LIS after cardiac surgery reflexes in a right way postoperative pulmonary changes.

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A.552 Sedation after coronary artery bypass surgery

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Background: In the first hours after CABG-surgery the patient will often present with haemodynamic instability. This possibly increases the risk for postoperative myocardial ischaemia. Adequate postoperative sedation is therefore indicated until the patient has been stabilised (1) This study compares the quality of sedation and the haemodynamic effects of propofol, midazolam and diazepam in these first hours after CABG-surgery

Methods: 45 patients, scheduled for primary CABG, were included. Preoperative anaesthetic regimens were standardized. Postoperatively patients were allocated randomly to three groups (N = 15). Two groups received double-blind either propofol or midazolam by continuous infusion The third group was given diazepam 5 mg boluses on a p r n. basis (max 20 mg in the first four hours) All patients were sedated for at least the first four hours postoperatively, titrating infusion-rates to maintain patients at sedation-level 3–4 on the Ramsay sedation scale

Results: Adequate sedation was achieved during 78 6% of the period for propofol, during 71 4% for midazolam and 66.7% for diazepam. After stopping sedation spontaneous ventilation resumed fastest in the midazolam group (after resp 283 minutes for midazolam, 353 minutes for propofol and 485 minutes for diazepam). These differences are not statistically significant During the first four postoperative hours diazepam had for 55% of this period a pulse-rate >90 beats/min. This is significantly longer as compared with both midazolam (34%) ($p = 0\ 01$) and to propofol (40%) ($p = 0.05$). Propofol exceeded for the shortest time-interval the maximal systolic target value of 120 mmHg (12.6%), although this was not significant compared with midazolam (17.6%) and with diazepam (23 1%). Patients given diazepam had a significantly greater amount of postoperative blood-loss (567 ml), as compared with patients given propofol (445 ml) ($p = 0.05$), and patients given midazolam (409 ml) ($p = 0\ 03$).

Discussion: Propofol and midazolam provided a comparable quality of sedation. After stopping sedation patients given midazolam resumed spontaneous ventilation quickest. As compared with diazepam both propofol and midazolam provided an haemodynamically more stable sedation, with a significant reduction in heart-rate and less postoperative blood-loss.

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A.553 B-mode echography in the diagnosis of radiological maxillary sinusitis

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Goal of the Study: Nosocomial maxillary sinusitis is a complication of nasotracheal intubation (1) Doing a CT scan (CT), which is the gold standard for the diagnosis of RMS, can be difficult in instable ICU patients. The B-mode E has good specificity and sensibility (2), but ICU patients were not evaluated. The aim of this prospective study was to assess the B-mode E in the diagnosis of nosocomial RMS

Materials and Methods: 18 consecutive ICU patients, oro-trachealy intubated and recuiring a CT were studied. In everyone were performed CT paranasal sinuses slices and a E E was realised with a 3.5 Mhz probe, in the canine fossa, using longitudinal and transversal sections, in dorsal decubitus and half seated positions. E was performed by the 2 same intensivists who were not aware of the CT result When the posterior sinus wall was seen, E was defined as positive

Results: 36 sinus were studied *CT* showed 15 empty sinus cavities, 11 mucosal thickening (2 of them with an virtual sinus cavity), 6 air fluid levels and 4 complete opacities *E:* the feasibility was 100%, 26 were negatives and 10 positives.

CT scan	RMS–	RMS+
Positive echography	2	8
Negative echography	24	2

For E: sensibility was 80%, specificity 92%, positive predictive value 80% and negative predictive value 92%.

Discussion: Our results shown that performance of E observed in non ICU patients is verified in ICU patients (2). We had 2 false positive because this technique can't differentiate a total filling of the sinus cavity by a mucosal thickening or a liquid (mucosal or purulent) We did not compare these morphologic exams to the bacteriological analysis of the sinus aspirate, because few of our patients had clinical criteria for an infectious sinusitis. More inclusions are needed to study this point.

Conclusion: Bedside B-mode E in the diagnosis of RMS is easy and reproducible. To our opinion it could be an alternative to CT in the diagnosis of nosocomial RMS in unstable ICU patients

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A.554 Acute renal failure in the ICU

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Background: This study was conducted in order to compare two different groups of patients with ARF in the ICU. The association with multiorgan failure (MOF) and the six months survival rate were also investigated

Materials and Methods: Since 1994 our ICU patients with ARF have been assigned to one of two groups *Postoperative ARF* (ARF occurring in a patient within 72 hours after surgery) and *non-operative ARF* (as occurring after major infections) Only patients in need of renal replacement therapy (RRT) were included. Using a clinical database (REGINA®), age, sex, length of stay, diagnosis and therapeutic interventions (including ventilator days and days with RRT) were prospectively registered. Since January 1996 all patients have been scored (after 24 h) using the SAPS II severity scoring system (1) and with a daily simplified therapeutic intervention score, NEMS (2) Follow up of deaths occurring after discharge was possible by searching the Norwegain health registry

Results: 146 patients have been included in the 46 months period from January 1994 until October 1997, 72 with postoperative ARF and 76 with non-operative ARF Differences (mean ± SEM or %) between the two groups are given in table 1.

Table 1

	Postoperative ARF (n = 72)	Non-operative ARF (n = 74)
Age (years)	71.9 ± 1 3	55 9 ± 2 3
ICU stay (days)	9 5 ± 1.0	13 7 ± 1 7
Ventilator days	8.0 ± 1.0	12 0 ± 1 7
RRT (days)	6 2 ± 0.9	10 3 ± 1 6
SAPS II	56 1 ± 2 1	65.1 ± 3 4
NEMS/ICU stay	329 ± 34	480 ± 65
MOF (%)	76.3%	88%
ICU survival	54 1%	49 3%
6 months surv	37 5%	37 3%

The SAPS II estimated hospital survival was 42% for the postoperative ARF group and 23% for non-operative ARF

Conclusions: Most patients with ARF also have MOF in the ICU, and this combination still have a high mortality. Patients with postoperative ARF patients are older but less sick compared to non-operative ARF No significant differences in six months survival rate could be found, indicating that age more than severity of disease determines long term survival.

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A.555 Pancreatitis-associated protein reveals protective effects on pulmonary vasculature

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Introduction: Severe pancreatitis is often complicated by acute lung failure. It has been demonstrated that a specific pancreatic secretory protein is elevated during pancreatitis in the blood (200–1400 ng/ml) [1]. The expression of PP correlates with the severity of pancreatitis but increased PP levels prevented lethal pancreatitis in rats. Aim of this study was to investigate potential protective effects of PP on pulmonary vasculature after inflammatory PMN activation with fMLP.

Material and Methods: The experiments were performed in isolated and ventilated rabbit lungs which were perfused with 200 ml of Krebs-Henseleit buffer with a constant flow of 150 ml/min in a recirculating system It was tested whether pretreatment with PP (260 ng/ml; n = 9 or 500 ng/ml; n = 2) prior to fMLP injection influences pulmonary artery pressure (pap) and edema formation as assessed by lung weight gain

Results: Baseline values of pap were 8.0 ± 1.7 mmHg fMLP application resulted in an acute significant ($p < 0\ 01$) increase of pap (26 1 ± 6 1 mmHg). After pre-treatment with PP the pressure response due to the fMLP challenge was dose dependently reduced to 14.6 ± 2.3 mmHg (PP 260 ng/ml; $p < 0.05$) and 8 8 ± 3.9 mmHg (PP 500 ng/ml), respectively. Lung edema formation occurred in the fMLP group but was absent after PP-treatment in either concentration.

Conclusion: PP did prevent fMLP induced vasoconstriction and edema formation in the lung These findings point towards a protective effect of PP on PMN mediated lung injury. Elevated levels of pap during pancreatitis could reflect a compensatory organ protective mechanism Further studies are required to elucidate the pathophysiological impact of PP.

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A.556 Partial liquid ventilation, positive end-expiratory pressure and nitric oxide inhalation in an animal model of acute lung injury

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Background: Partial liquid ventilation with perfluoro-carbons and PEEP lead to a recruitment of collapsed alveoli, thereby improving arterial oxygenation in acute lung injury (ALI). Inhalation of NO can further increase PaO_2, depending on the number of well-ventilated lung segments We compared the effects of PEEP and partial liquid ventilation, each with and without inhaled NO on gas exchange and hemodynamics in experimental ALI.

Methods: ALI was induced in seven pigs (25 ± 5 kg BW) using a saline lung lavage model Gas exchange and hemodynamic parameters were determined at two levels of PEEP (5 cmH_2O and 15 cmH_2O) before and after initiation of partial liquid ventilation (10 ml/kg BW perfluoro-carbon, FC3280®, 3M), each with and without the combined inhalation of 10 ppm NO. Data are presented as mean ± SD, statistical analysis was performed using ANOVA for repeated measurements followed by Bonferoni's multiple comparison test.

Results: Significant changes in cardiac output (CO) and PaO_2 were observed only at a PEEP level of 15 cmH_2O during mechanical ventilation as well as partial liquid ventilation. Inhalation of NO had a distinct, although not significant effect on PaO_2 without affecting CO The venous admixture (Q_{VA}/Q_T) improved due to inhaled NO, PEEP and partial liquid ventilation, while all studied hemodynamic parameters remained substantially unchanged when compared to ALI.

	PEEP [cmH_2O]	NO [ppm]	PaO_2 [mmHg]	CO [l/min]	(Q_{VA}/Q_T) [%]
ALI	5		43 ± 7	6.1 ± 2 2	66 ± 8
	5	10	104 ± 79	5 0 ± 2 0	46 ± 14*
	15		334 ± 139*	3 9 ± 1 4*	23 ± 11*
	15	10	438 ± 75*	4 2 ± 2 2*	16 ± 3*
P	5		90 ± 38	4 8 ± 1 5	38 ± 7*
L	5	10	146 ± 89	4 9 ± 2 5	35 ± 13*
V	15		291 ± 148*	3 7 ± 1 4*	21 ± 6*
	15	10	317 ± 147*	3 7 ± 1 8*	19 ± 5*

* $P < 0\ 05$ when compared to ALI

Conclusions: We conclude that the application of high levels of PEEP can be as effective as partial liquid ventilation with small doses of perfluorocarbon in improving PaO_2 and Q_{VA}/Q_T in a saline lung lavage model of ALI.

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A.557 Predicting the patient's response to changes in mechanical ventilation: a comparison of physicians and a physiological simulator

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Background and Goal of Study: Changes to ventilator settings are part of the normal management of mechanically ventilated patients on the intensive care unit (ICU). Physiological simulations have provided useful predictions of blood gas responses to interventions in mechanical ventilation [1]. We have developed a physiological simulator (The Nottingham Physiology Simulator: NPS). In order to have value as a clinical predictive tool, the simulator needs to be consistently more accurate than a physician. This study aimed to compare the ability of the NPS and ICU physicians to predict changes in arterial oxygen tension (*PaO_2*) after alterations were made to ventilator settings.

Materials and Methods: The NPS is a computer simulation of original multi-compartmental physiological models We collected 25 data sets from mechanically ventilated ICU patients before and ten minutes after changes had been made in ventilator settings (inspired oxygen fraction and minute volume) Each data set included arterial blood gas analysis, ventilator settings, haemoglobin concentration and temperature. The simulator and 6 ICU consultants were provided with the patients' pre-intervention data sets and details of changes in ventilator settings Each provided predictions for changes in *PaO_2*

Results and Discussion: Mean magnitude of change of FiO_2 was 0 15 (SD 0.06) and mean magnitude of change of minute volume was 700 (SD 1000) ml. Mean absolute change in PaO_2 was 5.95 (SD 3.23) kPa. Values in the table are given for the mean absolute size of error (bias) for the NPS and the 6 ICU consultants (1–6). A negative value thus represents an underestimation of the size of change in PaO_2 and vice versa The scatter of error sizes is described by the 95% confidence interval of the bias (CI_{95}). The NPS was more accurate and consistent than any of the six ICU consultants.

	NPS	1	2	3	4	5	6
Bias (kPa)	0.3	−3 2	−1.4	−2 8	−1.3	−3 6	−0 7
CI_{95} (kPa)	± 0.4	± 1.3	± 0 7	± 1 2	± 1 2	± 1 2	± 1 1

Conclusion: The simulator may prove to be a useful predictive tool in the management of ventilation on ICU

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A.558 Consecutive sucralfate 0.7% aspiration into the lungs of rats: acute, subacute and chronic histological effects

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Background & Goal of Study: Aspiration of gastric contents continues to be a concern of physicians involved in the care of critically ill patients. Previous researches have focused on the single aspiration of sucralfate in various concentrations and amounts (1, 2) But recurrent events of aspiration are more likely to happen in critically ill patients. The aim of this study was to evaluate acute, subacute and chronic histologic effects of recurrent % 0.7 sucralfate aspiration.

Materials & Methods: 24 Sprague-Dawley rats were randomly divided into two groups (Control group, (n: 6); study group (n: 18)). Simulated aspiration of 0.5 ml/kg either % 0.7 sucralfate or % 0.9 normal saline with 24 hours interval for 3 days were induced by direct tracheal instillation. Control and study groups were divided into A, B, and C subgroups. Animals in subgroubs A (Acute), B (subacute), C (Chronic) were killed respectively, 4 hours, 7 days, 21 days after the last aspiration to evaluate acute, subacute and chronic histological changes of airways.

Results: In the control animals, there were no significant difference ($P > 0.5$) in histologic findings in the acute subacute, and chronic periods. In the acute period of the study subgroup (4th hour), there were significantly different ($P < 0.5$) acute inflammatory reactions, atelectasis and edema at any time interval studied. In the subacute period of the study subgroup (7th day), there were significant ($P < 0.5$) chronic inflammatory reactions. These chronic inflammatory reactions were not significant in the 21st day among other subgroups.

Conclusion: Recurrent 0 7% low volume sucralfete aspiration produced significant inflammatory airway lesions in the acute period These abnormalities resolved without any chronic progression in the chronic period

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A.559 Bronchoalveolar lavage with a diluted surfactant suspension before surfactant instillation improves the effectiveness of surfactant therapy in experimental acute respiratory distress syndrome

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Goal of the Study: To assess whether bronchoalveolar lavage (BAL) with a diluted surfactant suspension prior to surfactant instillation prevents the only transient improvement in lung function as reported after surfactant instillation in severe acute respiratory distress syndrome (ARDS) [1]

Materials and Methods: Adult male Spraque-Dawley rats underwent repetitive whole lung saline lavage to induce acute lung injury.[2] Then, animals were randomly divided into six study groups: the first group received surfactant (150 mg/kg) within 10 min after the last lavage (early treatment), whereas in the other five groups mechanical ventilation was continued for 3 h before treatment (late treatment). Treatment consisted of: surfactant instillation (150 mg/kg); BAL with saline; BAL with a diluted surfactant suspension (2.5 mg/ml); BAL with saline, immediately followed by surfactant instillation (150 mg/kg); and BAL with a diluted surfactant suspension (2.5 mg/kg), immediately followed by surfactant instillation (150 mg/kg)

Results: Blood gases were measured for 6 h and then BAL was performed to measure protein concentration and surface tension properties Mean PaO_2 values increased immediately after surfactant instillation to pre-lavage values and remained stable only in the group that received surfactant immediately after lavage procedure and the group that underwent BAL with a diluted surfactant suspension prior to surfactant instillation

Conclusion: BAL with a diluted surfactant suspension prior to surfactant instillation at a later time point in lung injury resulted in a stable improvement of lung function. This improvement is comparable with the results seen after surfactant instillation immediately after lung lavage

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A.560 Mechanical ventilation during closed system suctioning

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Background & Goal of Study: Closed systems for tracheo-bronchial suctioning (CSS) are superior to open suctioning with regard to gas exchange and hemodynamics. However, the interaction of modern ventilators and CSS regarding preservation of PEEP and ventilation has not been described yet [1]

Material & Methods: We did a bench test evaluation of a 14F closed tracheal suction system and four different ICU ventilators Our lung model had an FRC of 900 ml, compliance was 29 ml/mbar and resistance was 12 mbar/l/s. Suction was 0.7 Bar against occlusion. Against atmosphere, flow through the system was 341/min. We measured pressure and flow at the Y-piece and in the artificial trachea with two Bicore CP 100 pulmonary mechanics monitors. We investigated tube sizes 7.0, 7 5, 8 0 and 8 5 mm I.D. and volume (VCV) and pressure constant ventilation (PCV) with PEEP = 12 mbar, I·E ratio = 1:1, f = 15/min, minute ventilation (MV) = 101/min or inspiratory pressure = 21 mbar above PEEP Measurements were taken for 15s before (baseline) and after introducing the suction catheter and during continuous suctioning.

Results & Discussion: 1. Introducing the suction catheter during PCV led to a reduction in MV which depended on tube size. Auto-PEEP developed with 7.0 and 7.5 mm tubes only and was higher with VCV than with PCV. 2 With PCV and tubes of 8.0 and 8.5 mm PEEP was maintained during suctioning. 3. With PCV, FRC was maintained whereas it was fully (7.0 and 7.5 mm) or partly (8.0 and 8 5 mm) evacuated with VCV. 4. With PCV and 7.0 and 7.5 mm tubes, there was no ventilation during suctioning whereas with 8.0 and 8.5 mm tubes we found a MV of 7.3 and 9.51/min, respectively. With VCV, there was no relevant ventilation. A sensitive trigger was essential for PEEP upkeep and ventilation during CSS.

Conclusions: With a 14F catheter, only pressure constant ventilation with an active inspiratory trigger and a 8.0 mm I.D. or bigger tracheal tube maintained FRC and ventilation during suctioning.

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A.561 Induction of chromosome aberrations in peripheral blood lymphocytes after short-term inhalation of nitric oxide

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Background and Goal of Study: Inhalation of nitric oxide (INO) leads to vasodilation of pulmonary vasculature in ventilated regions of the lung resulting in selective pulmonary vasodilation. The clinical use of INO, although not formally approved as a drug, is widespread. NO may rapidly form nitrogen dioxide (NO_2) in an oxygen containing gas mixture. NO_2 has been shown to induce chromosome aberrations and mutations in both animal and bacterial test systems. A widely used end-point to evaluate the potential of a chemical agent to induce somatic mutations in exposed individuals, is measurement of chromosome aberration frequencies in cultured human peripheral blood lymphocytes. We investigated whether a 2-hour exposure to NO would increase frequencies of cells with chromosome aberrations in peripheral blood lymphocytes of human volunteers We also studied the effect on liver, kidney and haematological routine laboratory measurements.

Materials and Methods: Ten volunteers were exposed to inhaled NO 40 parts per million (ppm) for 2 hours. Pre- and post-exposure blood samples were analysed for chromosome aberrations using a chi-square probability distribution.

Results and Discussion: The proportion of cells from the pre-exposure samples from the volunteers all fell within the normal range with respect to structural aberrations (without and with gaps) No statistically significant differences ($p \leq 0$ 05) were observed between frequencies of aberrations in cultures established from the pre- and post-exposure samples No clinically significant alterations in kidney, liver or haematologic laboratory parameters after the exposure could be detected

Conclusion: This study demonstrates, in healthy adult volunteers, that a 2-hour exposure to inhaled nitric oxide 40 ppm in 30% oxygen, results in no detectable increase of chromosome aberrations in cultures established from peripheral blood lymphocytes in samples isolated prior to inhalation and 60 minutes after discontinuation of inhalation

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A.562 Resonant frequency in ARDS using superimposed high-frequency jet-ventilation

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Background and Goal of the Study: The mechanisms how high-frequency (HF) jet-ventilation techniques work have not been resolved completely (1, 2). Animal models lead to the assumption that HF ventilation with respiratory rates close to the resonant frequency (RF) could improve oxygenation The RF is achieved by the HF-part of the ventilation and may improve oxygenation (3).

Materials and Methods: 1 patient with ARDS was studied using SHFJV characterized by the simultaneous application of a low-frequency and a high-frequency jet-stream The RF was found by measuring airway pressure amplitudes inside the endotracheal tube during a stepwise increase of the HF pulsation's. The pressure changes were recorded and wave forms analyzed The area with the largest amplitudes represented the respirator setting were HF-rate was close to RF RF was determined at normal pulmonary function and during increasing pulmonary insufficiency due to pneumonia The measurements were continued until the patient regained normal lung function

Results: The results are presented in the following table.

Day	Murray Sc	Pa02/FiO2	RF
1	1	209 5	730
5	2 3	140 8	630
7	3 3	73 6	500
10	3	250	600
11	2	341 3	730

Discussion: The invasiveness of mechanical ventilation correlated with increasing pulmonary insufficiency and determined RF shift to a lower frequency. These changes correlated with the Murray Score However, improvement of pulmonary function was accompanied by a shift of RF back to the original higher frequency.

Conclusion: This presented case demonstrates that RF does change when lung function deteriorates and may be markedly lower than during normal lung function As RF may change daily it has to be determined regularly to set HF-rate for optimization of gas exchange.

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A.563 Superimposed high-frequency jet-ventilation combined with inhalation of nitric oxide in ARDS

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Introduction: Inhaled nitric oxide (NO) reduces pulmonary hypertension in severe ARDS and improves arterial oxygenation by redistributing blood flow to areas with a nomal ventilation/perfusion ratio (1) As high peak inspiratory pressure (PIP) may contribute to pulmonary damage ventilatory strategies like high-frequency (HF) ventilation search to minimize PIP This study was designed to evaluate the combined benefits of superimposed high-frequency jet-ventilation (SHFJV), a new HF jet-ventilation technique, with addition of inhalational NO

Methods: 10 patients with severe ARDS were evaluated. All patients where ventilated with a conventional respirator (Evita, Drager Germany). The indication for SHFJV was a Horrowitz Index below 100. An electronic prototype jet-ventilator (Alexander 1, Reiner, Austria) used for SHFJV provided simultaneous low- (14–20/min) and high-frequency (400–600/min) jet-streams, which were applied with a special jet-adapter For application of NO we used the Pulmonox mini (Messer Griesheim, Austria) including a specially developed computer software for precise addition of NO (10 ppm) to the HF jet-stream during inspiration (2). After 3 hours of jet-ventilation we additionally applied NO

Results: PaO_2/FiO_2 and Horowitz index increased during SHFJV and NO application, while PIP could be reduced maintaining the same levels of CO_2 (Table 1)

Table 1

	CPPV	SHFJV	SHFJV and NO
Oxygenation	19 7	16 8	13 9
Horrowitz	96	118	149
PIP (cm H_2O)	34	30	30

Conclusion: The beneficial effect of SHFJV on oxygenation can be combined with the selective effects of inhaled NO. Thereby, impaired pulmonary function can be further improved.

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A.564 A new high-frequency jet-ventilation technique in a patient with ARDS

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Introduction: High-frequency (HF) jet-ventilation has been introduced by Klain et al and is utilized as alternative ventilatory modality for patients during laryngeal surgery or pulmonary insufficiency (1) Here we report about a patient with ARDS, where superimposed HF jet-ventilation (SHFJV), an advanced jet-ventilation technique, applied with a special jet-adapter, considerably improved oxygenation

Case: A 44 yr old man was admitted to a surgical intensive care unit because of severe sepsis due to intrabadominal infection Subsequently, adult respiratory distress syndrome developed (Murray score 3 5) and the patient was ventilated with FiO_2 0 7, I E = 1, PEEP = 15 cm H_2O, Ppeak = 32 cm H_2O when HF ventilation was initiated on the 6th day after admission to the ICU. A new jet-ventilation technique, superimposed HF jet-ventilation (SHFJV), was utilized SHFJV was characterized by the simultaneous application of a high-frequent and a low-frequent jet stream via two separate small-bore cannulas using a special jet-adapter, which was connected to the conventional endotracheal tube. Settings of the electronic prototype jet-ventilator (Alexander I, Reiner, Austria) and airway pressures were comparable with the preceding conventional ventilation except the high-frequency rate set to 500/min and the low-frequency respiratory rate set to 20/min SHFJV resulted in a considerable increase in pO2 levels from 114 to 334 mmHg (+192%) within one hour and high FiO_2 was substantially reduced. SHFJV also enabled adequate CO_2-elimination with pCO_2 levels decreasing from 38.5 to 30 8 mmHg. Heart rate (98 *vs* 101 b/min), arterial blood pressures (MAP 69 *vs* 72 mmHg) and cardiac output (8 39 *vs* 8.52 L/min) did not change Likewise, mean pulmonary artery pressure (33 *vs* 35 mmHg) and pulmonary capillary wedge pressure (17 *vs* 17 mmHg) remained unaffected. No ventilator associated complication was observed and SHFJV was continued. However, the patient died due to multiple organ failure on the 8th day

Conclusion: This case of ARDS shows, that SHFJV by combining high-frequency and low-frequency jet-ventilation appears to be an effective ventilatory support to improve impaired oxygenation Furthermore, SHFJV can be performed over several days because it facilitates normal CO_2 elimination

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A.565 A new method of quantification of ventilated areas: preliminary data

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Background & Goal of Study: This pilot study reports of the unprecedented possibility to objectify the recruitment of atelectatic areas with a mobile CT, in patients who are served superimposed high-frequency jet-ventilation (SHFJV).[1]

Material & Methods: After institutional approval four patients, three male and one female with a mean age of 52 years (ranging 21 to 83 years) received SHFJV for four hours by a prototype of a new electronic jet ventilator named ALEXANDER 1. Blood gas analyses were taken every half hour during the whole study period A thorax CT (mobile CT, Philips Tomoscan M, Netherlands), was taken of every patient before and after the period of ventilation with the possibility of 3D reconstruction The ventilated areas of each thoracic CT-picture were digitally remastered and volumetricly measured down to one ccm by a serial scan of the lungs We were always using the same parameters a matrix of 512 to 512, a zoom factor of 1.4, slicethickness 1.0 cm, pitch 1.0 cm, a trash hold of –400 to –1000 HE. Additionally, a high resolution CT (HR-CT) was performed of every patient's lungs (slicethickness 0.2 cm, pitch 1.5 cm, same trash hold and same matrix as in the serial scan) before and after jet-ventilation, in order to detect any alteration of the parenchyma or changing of the diameters of the bronchi. Data export was performed via DICOM III on a Philips Easy Vision 2.1.2 Sun Sparc Station 5

Results & Discussion: The situation of every lung improved The average amount of the improvement of the ventilated areas were 329 ccm, which represented an average increase of 11.7% In analogy of these values, we saw that the Pa02 measurements of the arterial blood gas analyses were improving too. The average increase of the Pa02 value amounted to 40.4% within the period of SHFJV, meaning that the improvement of the ventilation (recruitment of the atelectatic areas) leads to a better oxygenation Regarding the HR-CT, we saw no dilatation of the bronchi, but a decrease of the atelctatic areas within a reduction of the ground glas obesity

	Pat 01	Pat 02	Pat 03	Pat 04
Ventilated area				
before (ccm)	4398	2233	2524	3265
after (ccm)	4734	2764	2613	3525
difference (ccm)	336	531	189	260
percent (%)	7.6	23.7	7.48	7.91
Pa02				
before (ccm)	90.6	102.1	101.2	120.6
after (ccm)	140.7	143.2	146.4	152.8
difference (ccm)	50.1	41.1	45.3	32.2
percent (%)	50.1	40.2	44.7	26.6

Conclusion: The improvement of the ventilation and oxygenation can be umpirely objectified with this method. This possibility visualizes the advantages of superimposed high-frequency jet-ventilation.

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RESUSCITATION AND EMERGENCY MEDICINE

A.566 Circulatory effects of hypertonic saline/dextran during uncontrolled intra-abdominal bleeding

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Background and Goal of Study: Penetrating trauma of the torso frequently results in injury to the large vessels leading to death from exsanguination.

Materials and Methods: Ten minutes after a 5-mm long laceration was produced in the infrarenal aorta, 16 ketamine anaesthetized pigs were randomized to receive either no fluid or a 1 minute infusion of 4 mL/kg hypertonic saline/dextran (Medisan Pharmaceuticals) The experience gained from previous studies has indicated that approximately 26 mL blood per kg body weight is lost from the circulation in this type of injury (1). The hemodynamics were studied using arterial and pulmonary artery catheters and ultra-sonic (Transonic®) flow probes placed over the portal vein, the left renal artery, and in the abdominal aorta below the renal arteries, proximal and distal to the aortic injury.

Results and Discussion: The bleeding stopped spontaneously after approximately 3 minutes (calculated as the difference between the flow rates in the upper and lower aorta) The bleeding decreased with a half-time of 41 sec. After the initial hemostasis, the bleeding started again in 6 of 8 animals receiving hypertonic saline/dextran. The total volume of blood loss amounted to 727 ± 331 mL in the control group and 1008 ± 214 mL in the treatment group The survival rate were 4 of 8 animals in the control group and 3 of 8 animals in the treated group. In all animals that died, the amount of blood loss did not differ from that in other pigs until the rebleeding started, and the animals then died due to rebleeding and consecutive shock.

The results of our study may have implications to the treatment of penetrating intra-abdominal injuries with suspected large-scale haemorrhage. The intravenous infusion of hypertonic saline/dextran rapidly increased the blood pressure and the start of rebleeding, resulting in an increased mortality. It therefore seems very important to give definitive treatment in the hospital within 30 min of the initial treatment with hypertonic saline/dextran.

Conclusion: Hypertonic saline/dextran fluid therapy improved the hemodynamic status but increased the risk of rebleeding

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A.567 Atypical clinical features of acute aortic dissection in an emergency department

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Background & Goal of the Study: It is admitted that the classical clinical presentation of aortic dissection is a sudden chest pain which occurs in 95% of the cases[1] But the symptoms seem extremely variable The goal of the study was to describe the different clinical manifestations of acute aortic dissection and to draw attention on the atypical forms

Patients & Methods: We reviewed all the acute aortic dissections diagnosed at the admission in the surgical intensive care unit over a six-year period. All the symptoms participating to the initial clinical presentation were recorded

Results: Among 71 patients admitted in the emergency department, 9 had a chronic aortic dissection and 59 shows acute symptoms All symptoms and atypical clinical features which could lead to an erroneous diagnosis are depicted in the table Classical chest pain was present in only 60% of the cases In 25% of the cases, pain was purely abdominal. 1 of these patients showed an elevation of the ST segment on EKG and 1 epigastric pain was relieved by nitroglycerine In 3 cases (2 strokes and 1 spontaneous paraplegia) the patients had isolated neurologic symptoms In 2 cases patients had congestive heart failure (CHF) with pulmonary oedema, related to acute aortic regurgitation 2 patients were admitted for unexplained shock 1 have been operated for an acute limb ischemia simulating arterial embolism This patient developed also a severe hypercapnia resulting from a mediastinal compression of right pulmonary artery and left main bronchus

Clinical manifestations

Symptoms	Incidence (n)	
	Total*	Atypical
Chest pain	37	0
Abdominal pain	21	15
Pericardial effusion	7	0
Shock	6	2
CHF	2	2
Stroke	3	2
paraplegia	6	1
Limb ischemia	2	1

* A patient could have several symptoms

Conclusion: Acute aortic dissection could be frequently ignored because of the missing classical chest pain. Non typical clinical manifestations are frequent (39%) and could lead to inadequate treatment

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A.568 Transcranial Doppler in resuscitation: pathological cerebral perfusion after CPR and delayed return of spontaneous circulation

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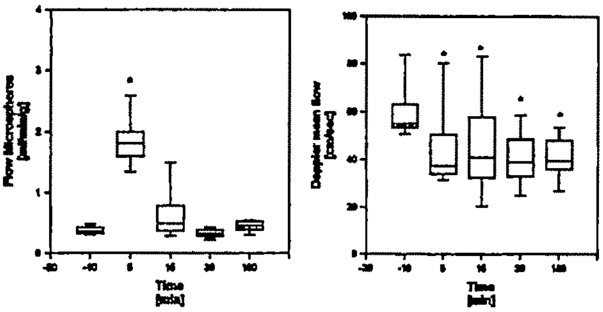
Background and Goal of Study: Monitoring of intracranial hemodynamics using transcranial Doppler-Sonography (TCD) may give information to optimize therapy after cardiopulmonary resuscitation (CPR) to avoid ischemic cerebral injury. The effects of cardiac arrest and CPR on cerebral blood flow (CBF) and TCD flow patterns were studied, especially after delayed return of spontaneous circulation (ROSC)

Materials and Methods: After approval by the local animal investigation committee 8 domestic pigs (23–30 kg) were investigated under general anesthesia. Before ($t_0 = -10$ min) cardiac arrest of 4 min, closed chest CPR of minimum 5 min and at $t_1 = +5$, $t_2 = +15$, $t_3 = +30$, $t_4 = +180$ min after ROSC TCD mean flow, Pulsatility Index (P.I.), Resistance Index (R.I.), CBF (microspheres), CO (thermodilution), HR, MAP, EEG and arterial blood gases were determined. The duration of CPR was depending on the time ROSC could be achieved.

Results and Discussion: Due to cardiac arrest electrical activity came to baseline within 45 sec 5 min after ROSC (t_1) CBF showed a significant increase ($p < 0.05$), as TCD mean flow decreased significantly ($p < 0.05$) compared to baseline (to) Under normoventilation CBF was normalizing at t_2 +15, t_3 +30 and t_4 +180, but TCD mean flow stayed significantly



deminuted. CO increased significantly at t_1+5 and stayed normal from t_2+15 until t_4+180. P.I. increased more than it would be expected by chance at t_1 +5, t_2 +15 and t_3 +30. Depending on short time CPR (group1) or long time CPR (group2) there is a significant difference ($p < 0.01$) in P.I.

Conclusions: Increased CBF, decreased TCD mean flow and increased P.I. after ROSC indicate an increase in intra-cranial pressure due to vasogenic brain edema depending on duration of CPR detected by Transcranial Doppler.

A.569 Effect of trauma and cisapride on gastric emptying

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Introduction: The proposed mechanisms for the delay in gastric emptying following trauma are difficult to study in a controlled manner in a human population. Prokinetic agents have been shown to increase GE in volunteers and experimental models. Cisapride (C) has been shown to increase gastric emptying in a rat model.(1) We investigated the effect of trauma and C, alone and in combination on GE in an animal model.

Methods: Twenty four male Sprague Dawley rats (weight 290–310 g) were fasted overnight. They were anaesthetised with ketamine 75 mg/kg and acepromazine 2.5 mg/kg i.m. A 22G iv cannula was inserted in a tail vein and 10 ml/kg 0.9% saline was given. Rectal temperature was monitored and normothermia maintained using an overhead heater. Gastric emptying was assessed in terms of % of a test meal emptied over one hour.(2) At time 0 a test meal of 3 ml (of known weight) was given via an orogastric tube. The animals were randomised into three groups of eight. Group 1 (controls) – no trauma, Group 2 – trauma immediately after feed (femoral fracture) and Group 3 trauma/and cisapride 3 mg/kg i.p 15 minutes later. All animals were euthanized one hour post feed and laparotomized. The stomachs were removed, weighed on an analytical balance then cut open, rinsed and weighed again. The % test meal emptied from the stomach in one hour was calculated for each group. Dunnetts Method was used to assess differences between the mean value for GE in the control group and groups 2 and 3 and comparisons for all pairs were made using Tukey-Kramer HSD. (alpha = 0.05)

Results: Results are expressed as mean ± SEM (table 1)

Group	% meal emp	SD	SEM
Control	83 375	4 1036	1 4508
Trauma	50 625	7 4438	2 6318
TR + CIS	77 9262	16 1426	5 7073

Gastric emptying was significantly decreased in the trauma group compared to control and the trauma/cisapride group There was no significant difference between control and the trauma/cisapride group.

Conclusions: Trauma delays gastric emptyingin this animal model and cisapride reverses this effect. This may have an application in the preoperative management of the trauma patient This study supports the contention that prokinetic agents promote gastric emptying in trauma.

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A.570 Emergency medicine on the Internet

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Current developments in medicine led to a large number of modern information systems Beside traditional printed and audiovisual media, working with computers is of increasing importance. Off-line systems (e.g. CD-ROM) and on-line systems are available. Easy access from workplaces in the office or at home, low costs and a wide range of information brought the Internet into the centre of interest during the last years. Providers of medical information include publishers of journals, organisations, universities and hospitals, hosts of congresses, physicians, industrial companies and commercial information providers. Many of these pages are of interest for the physician working in the field of emergency medicine. But the huge amount of data available on the Internet is not only of interest, it is also the source of a major problem with this on-line information system. How do you find what you are looking for?

Search engines find up to 10,000 pages somehow related to the topic of emergency medicine. To select the major sites providing information for the physician working in emergency medicine we used refined search criteria and selected the most interesting homepages Links to these sites are available at our homepage http://mailbox.univie ac at/~a5831mhc/ems html/ and can be easily accessed worldwide. All recommended sites are listed with short descriptions of their contents.

A.571 Aspiration in trauma

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Background and Goal of Study: Victims of major trauma are assumed to be at high risk of aspiration of gastric contents Whether the risk of aspiration comes from blood and debris from the upper airway or gastric contents, has not been determined. Determining where the major risk lies has implications for airway management We have examined the incidence and nature of aspiration in a group of trauma patients

Methods: 53 consecutive patients with major trauma who required pre-hospital endotracheal intubation by members of the Helicopter Emergency Medical Service in London were studied prospectively At direct larangoscopy the presence, amount (small, moderate, large), and nature of contamination visible around the vocal cords was recorded Post-mortems looking specifically for evidence of aspiration were requested on 17 patients who died within 4 hours of injury.

Results: There were 42 male and 11 female patients. Mean age was 41 (range 16–80) 44 (83%) had head injuries 29 had a Glasgow coma score of 3 and 39 scored 8 or below 21 survived and 32 died. 18 (34%) of patients had evidence of contamination at laryngoscopy. 15 had blood/debris from the upper airway and 3 had gastric contents. Of the 10 post mortems performed one confirmed aspiration of gastric contents, one confirmed aspiration of blood, 7 confirmed that no aspiration had occurred and one showed no evidence of aspiration where a moderate amount of blood had been seen at intubation.

Discussion: Contamination of the vocal cords was common but was mostly from the upper airway rather than gastric contents This is consistent with the findings of a study of 17 trauma patients who aspirated (1) Where a definitive airway (i.e. cuffed tracheal tube) is indicated but cannot be provided, a device which provides some protection from upper airway soiling (e g. the laryngeal mask airway) would be more appropriate than the conventional oropharyngeal airway which offers no protection from aspiration from debris from the upper airway (2).

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A.572 Prehospital tracheal intubation: a retrospective study of compliance with a set of criteria

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Introduction: Tracheal intubation before the admission to an emergency room is a key factor in the management of severely ill or traumatised patients. However, since this procedure is often performed by junior physicians, the indication for tracheal intubation has to be carefully standardised

Objective: The aim of this study was to evaluate the degree of compliance with a proposed set of criteria for tracheal intubation, in the prehospital management of severely ill or traumatised patients.

Methods: Patients over 16 years of age, intubated within fifteen minutes upon admission at the hospital were analysed retrospectively. Failure to comply with the proposed criteria and the reasons for intubation upon admission in the emergency room were reviewed

Results: During a 30 months period, from the 1st January 1995 to the 30th of June 1997, 4233 patients were admitted to our emergency room, 20.1% were transported by helicopter and 79.9% by ground transportation Prehospital intubation was performed in 555 cases (13 1%), while failure to intubate the patient occurred in 15 patients (2.7%). Among those, 10 died before admission.

Among patients we were not intubated at admission, 26 (0.7%) required emergency tracheal intubation immediately upon admission at the emergency room Reasons for emergency tracheal intubation upon admission included a) unsuccessful attempt to intubate the trachea at the site of injury (n = 5), b) worsening of the patient's condition (n = 8), c) information from additional investigation (n = 5), and d) inadequate evaluation at the site of injury (n = 8)

Conclusion: The number of patients for whom the proposed criteria for prehospital tracheal intubation were overlooked is small (0.18%). The decision not to intubate was made deliberately in all cases and can be regarded as mismanagement.

We therefore believe that the proposed criteria for prehospital tracheal intubation do no need to be changed since they allow for adequate management of the vast majority of severely ill or traumatised patients.

A.573 Survival of trauma patients who have prehospital endotracheal intubation without anaesthesia or muscle relaxants

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Background: In the UK it is current practice for paramedics to perform endotracheal intubation on trauma patients when the airway is compromised and basic airway manoeuvres fail Anaesthetic drugs and muscle relaxants are not used. We have investigated the outcome in a population of trauma patients who are intubated in the pre-hospital environment without drugs.

Methods: We looked retrospectively at the database of a physician led helicopter emergency medical service dedicated to trauma patients. We identified patients that had been intubated without drugs by paramedics and doctors and recorded whether they survived to hospital discharge.

Results: In a six year period 680 patients were intubated and airlifted from the scene. Data was available on 678 566 received anaesthetic drugs and/or muscle relaxants and 94 received none. One patient in the no drug group survived (1%). He had suffered a cardiac arrest after penetrating chest trauma and had an on scene thoracotomy to relieve pericardial tamponade.

Discussion: There is little evidence that endotracheal intubation improves the outcome in cardiac arrest patients (1, 2, 3). Our results suggest that this may also be the case for victims of trauma as virtually all patients intubated outside hospital without drugs died. In UK paramedic practice, non-drug assisted endotracheal intubation is a major part of extended training. The value of this intervention deserves further scrutiny.

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A.574 Resuscitation from cardiac arrest with adrenaline or vasopressin: systemic and regional effects during the post-resuscitation period in rats

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Background & Goal of Study: Using vasopressin (AVP) instead of epinephrine (EPI) improves vital organ perfusion (1) during resuscitation, but depression of myocardial function during the postresuscitation period (2) has been reported. Whether the mesenteric perfusion is affected, is unknown. We therefore determined jejunal mucosal PCO2 before cardiac arrest (CA) and 60 min after return of spontaneous circulation (ROSC)

Methods: 28 rats (450–500 g) were anaesthetised, ventilated, invasively monitored and a 5 Fr. paediatric tonometer was inserted into the jejunal lumen Precordial chest compression (PCC) at a rate of 200/min, using a thumper (Michigan Instruments) was started 4 min after onset of AC induced ventricular fibrillation (VF), continued for 4 min and followed by transthoracic DC defibrillation with 5 J. After 5 min of VF the rats randomly received AVP (0 8 U/kg) or EPI (90 μg/kg) i.v. Before CA and after 60 min of ROSC, right atrial oxygen saturation (SvO2) (OSM 3), arterial lactate (YSI 2300), arterial pH, PCO2 and tonometric PCO2 (PtCO2, IL 1302) were measured. PCO2 gap and pHi were calculated using standard formulas. Group means ± SD were analysed using Student's t-test.

	Before CA		60 min ROSC		
	EPI	AVP	EPI	AVP	p
MAP mmHg	146 ± 20	140 ± 18	87 ± 15	99 ± 12	0.058
SvO2 %	78 ± 7	73 ± 5	54 ± 8	63 ± 5	0 004
Lactat mmol/L	1.3 ± 0 2	1.1 ± 0.2	3 4 ± 0.7	2 5 ± 1 4	0.142
pH art	7.36 ± 0 03	7 37 ± 0 04	7 23 ± 0 06	7 25 ± 0 10	0 512
PtCO2 mmHg	56 ± 6	54 ± 3	73 ± 7	65 ± 7	0 035
PCO2 gap	17 ± 5	17 ± 3	34 ± 7	24 ± 10	0 059
pHi	7 21 ± 0 04	7 21 ± 0.03	6 97 ± 0.06	7 05 ± 0 08	0.049

Results (table) AVP and EPI increased coronary perfusion pressure during resuscitation to similar levels (48 ± 14 vs 40 ± 10 mmHg). 7 of 14 (AVP) vs. 12 of 14 (EPI) rats were successfully resuscitated (p = 0.132, Fisher's exact test).

Conclusions: Higher SvO2, lower PtCO2 and higher pHi might indicate that the use of AVP during resuscitation is associated with better systemic oxygenation and less mesenteric ischemia in the early postresuscitation period Whether this is due to increased perfusion, remains to be cleared

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A.575 Diagnostic value of troponin T as a biochemical marker of myocardial contusion

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Background and Goal of Study: The diagnostic delimitation of myocardial contusion is difficult because of nonspecifity of diagnostic tests Circulating cardiac troponin T (cTnT) is considered a highly sensitive and specific marker of myocardial cell injury [1] The purpose of this study was to investigate the value of cardiac troponin T (cTnT) measurement as a biochemical marker in the diagnosis of myocardial contusion

Material & Methods: Prospective study, involving one hundred-twenty-five (125) trauma victims (92 male, 33 female; age: 35.4 ± 19.2 years; ISS· 23 4 ± 16 0), who were admitted to our hospital during an one year period (01 10 1995–31 10 1996) In all patients the following diagnostic screening was performed: 12 lead ECG and transthoracic echocardiography at hospital admission (time "A"), CK and CK-MB as well as quantitative cTnT measurement at hospital admission (time "A"), after completion of diagnostic phase (time "B") and 24 h after hospital admission (time "C") Additionally, a qualitative cTnT bedside-test (TropT™, cut-off: 0.2 μg/l, test result within 20 min) was performed at time "A" and "B"

Results & Discussion: In 14 4% of the cases, Trop™-test was positive, there was a statistically significant correlation between the quantitative cTnT measurement and TropT™-test results ($p < 0.001$; sensitivity 1.0/0.86 – specifity 0.89/0.94 at time "A"/"B"). In 60.8% of the cases, a positive CK-MB/CK index (>5%) was found, but there was no correlation to quantitative and qualitative cTnT measurements The relationship between TropT™-test/CK-MB/CK index and TTE/12-lead ECG is shown in the following table:

	TTE		ECG	
	pathol	Normal	pathol	normal
TropT™ positive	2	13 ns	3	9*
TropT™ negative	9	83 ns	5	101*
CK-MB/CK positive	9	58 ns	5	65 ns
CK-MB/CK negative	2	38 ns	3	45 ns

*p < 0 008

Conclusion: Even in the early phase after trauma, cTnT has proven itself as a sensitive and specific biochemical marker of myocardial cell injury. Of clinical value is the qualitative TropT™-test.

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A.576 Prehospital care and survival in paediatric blunt trauma

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Background: The aim of this study was to compare the outcome of severe blunt trauma in children receiving prehospital care from either physician-staffed advanced life support (ALS) units, or from basic life support (BLS) units staffed by emergency medical technicians

Methods: The records of 288 children with severe blunt trauma who required intensive care in the regional level 1 trauma center, or who died from their injuries, were analysed retrospectively Patients were excluded if resuscitation at the scene was not attempted, if the level of prehospital care was unspecified, or if arrival at the level 1 trauma center was delayed beyond 150 minutes. Seventy-two patients met the inclusion criteria of BLS-, and 49 the criteria of ALS-prehospital care.

Results: A reduced mortality (22.4% vs. 31.9%) was seen in ALS group, which was more apparent in a "salvageable but high risk" subgroup, characterized by Glasgow Coma Scale (GCS) 4–8, Paediatric Trauma Score (PTS) 0–5, and Injury Severity Score (ISS) 25–49. However, a statistically significant difference was only seen when trauma severity was evaluated by the ISS.

Mortality and measures of injury severity

Measure		ALS group %	BLS group %	P-value
Overall mortality		22 4	31 9	NS
GCS	3	100	100	
	4–8	23 5	36 4	NS
	9–15	0	2 3	
PTS	<0	75 0	100	
	0–5	38 1	54.2	NS
	6–12	0	2.9	
ISS	<25	0	2 6	
	25–49	24 0	54 5	0 040
	50–75	100	83 3	

The trauma scores are were calculated on hospital arrival

Conclusion: An improved outcome in children with severe blunt trauma has been demonstrated when prehospital care is provided by physician-staffed ALS units compared with BLS units

ACUTE AND CHRONIC PAIN MANAGEMENT

A.577 Serotonin sensitizes primary afferent nociceptors to bradykinin

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Background & Goal of Study: Serotonin (5-hydroxytryptamine, 5-HT) is known to produce pain and hyperalgesia in the peripheral nervous system [1]. The method of spinal cord dorsal horn c-Fos immunohistochemistry has been shown to be a reliable marker for neuronal activity following noxious stimulation of primary afferent nociceptors [2]. The purpose of this study was to determine if bradykinin-induced dorsal horn c-Fos is enhanced after pretreatment with 5-HT at a concentration (10^{-6} M) which alone does not stimulate c-Fos expression

Materials & Methods: After institutional approval experiments were performed on anesthetized adult male Sprague-Dawley rats (weight 365–385 g). 100 μl each of either 5-HT 10^{-6} M, bradykinin 10^{-5} M, 5-HT 10^{-6} M + bradykinin 10^{-5} M or saline (control) was injected in rat left knee joints (n = 4 rats per treatment group). After 90 minutes the lumbar spinal cords were removed and immunostaining, according to the avidin-biotin peroxidase method of Hsu et al. [2], was performed on 45 μm spinal cord sections with a specific antibody to the c-Fos protein. Fos-like immunoreactivity was studied through L2 and L3 spinal segments by counting Fos-positive nuclei in the dorsal horn and taking ratios between ipsi- and contralateral sides Results are presented as mean ± SD and statistical one-way analysis of variance was used to compare the different groups.

Results: 5-HT alone did not show a statistically significant difference compared to control ($p = 0.744$), whereas bradykinin was significantly different from control (2.9 ± 0.7 vs. 1.2 ± 0.2, $p < 0.001$) and 5-HT administered together with bradykinin was significantly different from bradykinin alone (4 9 ± 1.0 vs. 2.9 ± 0.7, $p = 0\ 001$).

Conclusion: We have demonstrated that 5-HT enhances bradykinin-induced spinal c-Fos expression and possibly induces hyperalgesia by sensitizing nociceptors to chemically noxious stimuli in the rat knee joint. Additional pharmacological studies are being performed to determine the specific receptor subtype(s) involved in 5-HT-induced hyperalgesia.

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A.578 Effect of intrathecal agmatine on morphine-induced spinal analgesia in rats

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Background & Goal of Study: Agmatine is a primary amine recently discovered to be a clonidine-displacing substance, which is the endogenous ligand of alpha-2-adrenergic and imidazoline-receptors (1). It is well known that the intrathecal (IT) administration of clonidine which binds the alpha-2 adrenergic and imidazoline-receptors as well, results in antinociception and potentiates morphine-induced analgesia The purpose of the study was to investigate the possible antinociceptive effect of IT agmatine, and its interaction with IT morphine in inflammatory pain tests in rats

Materials & Methods: After institutional ethical approval intrathecal catheters were implanted, and two series of experiments were performed In single agonist studies, animals received agmatine (50 μg or 100 μg) before (pretreatment) or after (posttreatment) the carrageenan-induced inflammation Paw withdrawal latencies were obtained before carrageenan, 3 h after carrageenan, then 30 60 and 90 minutes later. In the second series rats received IT morphine (in cumulative doses of 1 μg, 4 μg and 5 μg) together with agmatine pretreatment or posttreatment Paw withdrawal latencies were determined 10 and 30 min after the morphine injections Groups were compared by ANOVA with $P < 0.05$ considered significant.

Results & Discussion: IT agmatine pretreatment dose-dependently decreased carrageenan-induced hyperalgesia and potentiated morphine-induced antinociception. Agmatine posttreatment alone caused a slight decrease in the hyperalgesia, but the higher dose significantly increased the efficacy of the lowest dose of morphine.

Conclusion: Based on the results obtained in this study, we conclude that the spinal administration of the endogenous ligand has beneficial effect on morphine-induced antinociception

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A.579 Drug interaction of intrathecal carbachol and clonidine in neuropathic pain model in the rat

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Background: Peripheral nerve injury may generate a syndrome of events (spontaneous pain, allodynia and hyperalgesia), that includes poor response to morphine and dependency of this pain state on intact sympathetic function Spinally delivered α2-adrenoceptor agonist and cholinergic agonist or cholinesterase inhibitors each have been shown to have actions attenuating the hyperalgesia in rat models.

Using an isobolographic analysis (1), We examined the spinal interaction between the α2-adrenoreceptor agonist clonidine and cholinergic agonist carbachol in a rat model of neuropathy.

Methods: Male SD rats were prepared with tight ligation of left lumbar 5 & 6th spinal nerves (2) and chronic lumbar intrathecal catheters Intrathecal dose-response curves were established for the antiallodynic effect of carbachol (0 1, 0 3, 1 0, 3 0 mg) and clonidine (0 3, 1.0, 3 0, 10 mg) alone to obtain the ED50 for each agent (fig 1). ED50 fractions (1/2, 1/4, 1/8, 1/16) of drug combinations of carbachol-clonidine were administered and thresholds for left hind limb paw withdrawal to von Frey hair application were assessed and converted to MPE. The ED50 of carbachol-clonidine combination was established and isobolographic analysis of the drug interactions was carried out.

Results: Intrathecal carbachol and clonidine alone produced dose-dependent reductions of tactile allodynia· ED50 66 ng (12–367 ng) and 39 ng (1–1452 ng), respectively. The log dose-responses were plotted from the peak effect of %MPE in each group of carbachol and clonidine (fig 1). The experimental ED50 (point B) for carbachol-clonidine mixture was found to be significantly below the theoretical additive ED50 (point A) (fig 2).

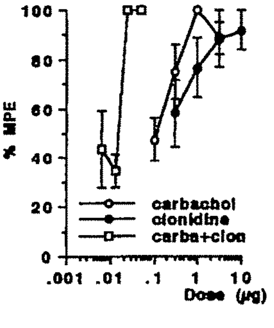

Fig 1 Dose response curves

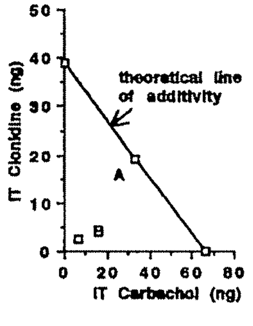

Fig 2 Isobolograph for synergism

Conclusion: The experiments suggested that intrathecal carbachol and clonidine alone produce a dose dependent antagonism on touch evoked allodynia and intrathecal carbachol is synergistic in the spinal level when combined with intrathecal clonidine in a rat model of neuropathy

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A.580 Comparison of morphine and tramadol in an animal model of trigeminal neuropathic pain

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Aim: The unique pharmacological features of Tramadol, an opiate-like analgesic, could make Tramadol the drug of choice for treatment of neuropathic pain syndromes. This assumption was evaluated in an animal model of trigeminal neuropathic pain, comparing Morphine to Tramadol administration

Methods: The experimental set-up consisted of six phases: acclimatisation, preoperative testing, surgery and development of the neuropathic pain syndrome, postoperative testing to assess trigeminal hypersensitivity and opiate analgesic effect, development of opiate tolerance, and finally postoperative testing to assess tolerance and cross-tolerance. The trigeminal neuropathic pain model is based on a chronic constriction injury to the infra-orbital nerve (Ion-CCI). Twenty-nine Sprague-Dawley rats received such a unilateral injury; ten control rats received unilateral sham-surgery. The presence of mechanical hypersensitivity was assessed using a mechanical stimulation test.

Results: Rats with an Ion-CCI showed hyperresponsiveness to a range of von Frey hair stimulations which was reduced both by Tramadol and Morphine. In sham-operated rats, the ratio between equi-analgesic doses of Morphine and Tramadol was 1/4.5 (ED50 3.23/14.1). Interestingly, in Ion-CCI rats this ratio was about 1/2 (ED50: 13.04/29.1). The effect of Morphine and Tramadol was predominantly reversed by Naloxone. Repeated Morphine administration led to the development of Morphine tolerance, but no cross-tolerance to Morphine was found after repeated Tramadol treatment. A 'lack of tolerance and cross-tolerance development' to Tramadol was observed.

Discussion: It is possible that, at the early postoperative time point, thanks to its combined opioid-non-opioid mode of action, the effect of Tramadol is only partly attenuated by the reduction of the opioid receptor responsiveness and the non-opioid mode of action remains fully efficient. Tramadol's inhibitory effect on the serotonine uptake could be responsible for this effect and might also be responsible for the relative lack of tolerance and cross-tolerance to Tramadol. Later in the postoperative period it is possible that the (−) enantiomer of Tramadol counteracts the analgesic effect of the (+) enantiomer at this later stage.

Conclusion: At the early postoperative time point, Tramadol had a relatively greater potency than Morphine to suppress the hyperresponsiveness in neuropathic pain conditions. At the late postoperative time point, the efficiency of Tramadol was reduced.

A.581 Experimental pain testing: how reproducible are the results?

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Background and Goal: Although experimental pain tests are widely used to test analgesic effects of drugs[1] or to assess pain susceptibility of individuals[2] there hardly exist any data on their reproducibility. We assessed the reproducibility of five different pain tests when performed on three different days on the same person and determined the circadian and inter-individual variation.

Methods: 6 female and 5 male healthy volunteers in the age of 22–26 years were tested on three separate days at the same day time with at least 48 hours apart. On Study day 1 two additional sessions were held at least 3 hours apart to assess circadian variability. The following experimental pain tolerance tests were applied: *Ice water pain*[2], maximal exercise *tourniquet ischaemia pain, pressure pain, heat pain* and *electrical pain* as well as *the reaction time* to acoustical signals. Maximal duration and pain rating by visual analogue scale (VAS) was continuously registered for the ischaemia and cold pain test with the area under the VAS vs. time curve (AUC) representing the perceived pain. After a trial testing to familiarize the volunteers with the procedure two test series were performed 15 minutes apart in each session. Coefficient of variations between the sessions were calculated for every volunteer and every test.

Results and Discussion: The mean coefficients of variation (standard deviation) of day-to-day, circadian and inter-individual variation are summarized below

	Day-to-day	Circadian	Inter-individual
Electrical Pain	0.31 (0.16)	0.15 (0.10)	0.38
Pressure Pain	0.09 (0.08)	0.09 (0.05)	0.22
Heat Pain	0.06 (0.02)	0.03 (0.02)	0.08
Ischaemic Pain	0.13 (0.09)	0.10 (0.10)	0.28
Cold Pain	0.11 (0.09)	0.10 (0.08)	0.22
Reaction Time	0.14 (0.08)	0.07 (0.05)	0.24

Electrical pain performed worst with an almost equal intra- and inter-individual variability probably due to a variable skin impedance. Heat pain tolerance, although best reproducible, hardly varies within the population.

Conclusions: Pressure Pain, followed by ischaemic and cold pain are best suitable to assess pain tolerance of an individual. The impact of circadian variation is probably negligible.

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A.582 Individual pain tolerance cannot be assessed by a single pain test

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Background and Goal: Cold Pain can be used to discriminate pain tolerant and pain susceptible individuals[1]. The aim of this study was to determine whether pain tolerance to one pain modality also implies pain tolerance to others. Thus four other experimental pain tests were compared with cold pain tolerance with regard to inter-individual variation and concordance between the tests.

Methods: 7 female and 8 male healthy volunteers in the age of 22–28 years were tested on three separate days at corresponding day time with at least 48 hours apart. Pain tolerance to the following experimental pain models were determined. *Ice water pain*[1], maximal exercise *forearm tourniquet ischaemia pain, pressure pain, heat pain* and *electrical pain*[2]. Reaction time on acoustical signals was measured as well. Maximal duration and pain rating by visual analogue scale (VAS) was continuously registered for the ischaemia and cold pain test with the area under the VAS vs. time curve (AUC) indicating the perceived pain. Sperman rank order correlation was used to calculate the correlation coefficient for all the pairs of tests with $p < 0.05$ considered significant. A histogram of the results for every test was used to describe the distribution of pain susceptibility in the test population.

Results and Discussion: Ischaemic pain susceptibility significantly correlated with cold pain ($r = 0.52$, $p = 0.046$) and (inversely) with heat ($r = -0.507$, $p = 0.051$) and pressure ($r = -0.582$, $p = 0.022$) pain tolerance. Heat and pressure pain tolerance were additionally correlated (0.696, $p = 0.003$). Electrical pain and reaction time were not significantly correlated with other tests. The AUC of cold and ischaemic pain revealed a bi-modal distribution within the population, whereas paintolerance as assessed by the other tests appeared normally distributed. In 7 of 15 volunteers the paintolerance results were not consistent between the five tests. Ischaemic and cold pain tolerance, that may allow discrimination between pain tolerant and susceptible individuals, were discordant in 3 of 15 volunteers.

Conclusions: The pain susceptibility is highly depented of the pain modality used. There is complete discordance from one test to another in many individuals despite a statistically significant correlation of pain tolerance between some tests.

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A.583 Effect of intravenous propofol on thermal pain thresholds

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Introduction: Propofol's analgesic properties remain controversial. Propofol in subhypnotic doses in adults has been shown to have an analgesic effect on somatic pain (1, 2). However others have found that propofol in sedative doses had no analgesic effect, although the reaction time was prolonged at the higher doses. In rats, propofol has been shown to have both an anti-analgesic and no anti-analgesic effect at subhypnotic doses.

The aim of this study was to investigate whether subhypnotic doses of propofol affected somatic pain thresholds. The combination of propofol in a subhypnotic infusion with thermal stimulation has never been studied before. We chose thermal stimulation as the pain stimulus because it is generally considered to produce the purest monomodal nociceptive stimulus.

Methods: This double-blinded placebo controlled randomized study was approved by our Institutional Review Board. Ten healthy volunteers were tested after familiarizing themselves with the testing procedures and stimuli. The 4 modalities tested were cold threshold, warm threshold, cold-induced pain threshold, and heat-induced pain threshold. Each modality was administered separately and randomly. Baseline temperature of the thermode was 32°C. The thermode delivered heat or cold stimuli to the subject's skin. Stimulation was discontinued by pushing a button. The thermode temperature changed at a rate of 0.7°C sec^{-1} (maximum 50°C, minimum 0°C) with 50 to 55 seconds between pain stimuli. Intravenous propofol doses were randomly administered to produce a constant effective site concentration of 0.0 (lipid emulsion), 0.2, 0.4, and 0.8 μg·ml^{-1} with a STANPUMP. Propofol was allowed to clear from the effective site for 30 minutes between cycles. Reaction time was tested by pressing a button in response to an audio signal ANOVA with repeated measures was used for analysis

Results: There was no statistically significant change in warm or cold detection threshold or heat or cold pain threshold Reaction time was not affected at the tested doses.

Discussion: The results suggest that propofol at subhypnotic concentrations does not have an analgesic or anti-analgesic effect Propofol also does not affect warm or cold threshold

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A.584 Gabapentin in chronic neuropathic pain (preliminary results)

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Background & Goal of Study: Anticonvulsant (ACD) and antidepressant drugs are used in combination for the treatment of chronic neuropathic pain Gabapentin, which has been reported to be effective in many kinds of neuropathic pain, may replace the older ACD due to the extremely low side-effect profile(*). The aim of the study is to analyse the use of gabapentin in a pain clinic during a year

Methods: Clinical records of patients who initiated treatment with gabapentin during the last year have been reviewed Several aspects have been analysed. Analgesic outcome assessment was made according to discharge, any improvement, no change, or impairment.

Results: 49 patients initiated treatment with gabapentin 63.26% were male. The mean age was 62.10 years Painful diseases were postherpetic neuralgia (21 cases), trigeminal neuralgia (7), central pain (7), phantom limb pain (4), postoperative or posttraumatic neuralgia (4), reflex sympathetic dystrophy (2), oncologic neuralgia (2), diabetic neuropathy (1) and stump pain (1) Only 6 patients were given gabapentin as first step treatment 43 patients received gabapentin after the initial analgesic therapy had failed. 77.55% of the patients showed clinical improvement (9 were discharged), 20.40% manifested no change and only 1 patient showed clinical impairment Of 21 patients suffering from postherpetic neuralgia, 14 showed clinical improvement, 2 were discharged and 5 showed no change. Of 7 patients receiving gabapentin for central pain treatment (5 vascular lesions, 1 traumatic brain injury and 1 traumatic spinal cord injury), 3 patients improved, 1 was discharged and 1 showed clinical impairment. Of 7 patients with trigeminal neuralgia, 3 were discharged and 4 showed clinical improvement Side-effects (drowsiness and myoclonia) occurred in 10.20% of patients and forced gabapentin interruption

Conclusions: Most patients showed any clinical improvement. A minority suffered from side-effects that, although not serious, forced treatment interruption Gabapentin may be considered a valid alternative for chronic neuropathic pain treatment, but only comparative studies will be able to establish reliable differences between gabapentin and the other ACD.

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A.585 Low systemic doses of ketamine reduce the temporal summation of nociceptive flexion (RIII)

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Introduction: In animals, both the responses of spinal nociceptive neurones and the amplitude of nociceptive reflexes increase progressively during repetitive high frequency (1–3 Hz) electrical stimulation of peripheral C-fibers. This "wind up" phenomenon which is due to the slow temporal summation of nociceptive signals in the spinal dorsal horn, is specifically reduced by NMDA antagonists such as ketamine. The aim of the present study was to evaluate in man, the effects of low systemic doses of ketamine on the central temporal summation of both the nociceptive flexion (RIII) reflex and pain sensation.

Methods: On two experimental days separated by 1 week, the RIII reflex elicited by electrical stimuli of the sural nerve at the ankle was recorded from the ipsilateral biceps femoris in 6 healthy volunteers. During each experimental day, we studied both before and after the randomized intravenous injection of 0.15 mg/kg ketamine or placebo· 1) the RIII reflex threshold; 2) the recrutement curve of the reflex up to the tolerance threshold, 3) the temporal summation of the reflex induced by repetitive electrical stimuli (frequency· 1 Hz; duration 15 s, intensity. 1.2 × the reflex threshold); 4) the modifications of pain, quantified by means of an visual analog scale, during the series of high frequency stimuli.

Results: The RIII reflex threshold, the tolerance threshold and the recrutement curve of the reflex were not significantly altered after the injection of ketamine or placebo. During the series of 15 electrical stimuli at 1 Hz, a significant increase of both the reflex responses and pain sensation was observed These facilitatory effects due to the temporal summation of nociceptive signals were significantly reduced after ketamine but not significantly modified after placebo.

Conclusion: The present results show that temporal summation of nociceptive stimuli facilitates the Aδ fibers elicited RIII reflex The effects of ketamine suggests that such a phenomenon is related to the "wind up" described in animals. Thus, the RIII reflex might constitute an interesting tool to quantify and analyse in man, the mechanisms underlying the central temporal summation of nociceptive inputs, which probably have a significant role in the pathophysiology of both acute and chronic pain syndromes

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A.586 Effect of naloxone and ketamine on primary and secondary hyperalgesia in humans

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Background and Goal of Study: Peripheral tissue damage results in sensitization of dorsal horn neurons This is manifested clinically as allodynia and hyperalgesia (1) Injury induced sensitization of dorsal horn neurons has been implicated as an important contributor to both acute and chronic pain states (2). Ketamine binds noncompetitively to the NMDA receptor, thereby inhibiting the action of glutamate which increases spinal hypersensitivity It is not clear, whether ketamine exerts its effect solely by inhibiting excitatory amino acids, or if there is a degree of opioid interaction involved The aim of the study was therefore to investigate the effects of ketamine, with or without naloxone pretreatment, on pain and hyperalgesia after a burn injury in human volunteers.

Methods: Twentyfive male volunteers participated in the study. 1° burn injuries were induced on the right calf On 3 separate days, the subjects received a: naloxone followed by ketamine, b saline followed by ketamine, or c: saline only Pain ratings (VAS) and heat pain detection thresholds (HPDT) were determined on the burned and the unburned calf Areas of secondary hyperalgesia to punctuate and stroke stimuli around the burn injury were calculated.

Results: Ketamine reduced primary and secondary hyperalgesia with, and without pretreatment with naloxone As naloxone was injected before ketamine, a measure of opioid antagonism towards hyperalgesia was obtained Naloxone increased secondary hyperalgesia after burn injury. Side effects were frequent but clinically acceptable.

Conclusions: Ketamine, and ketamine preceded with naloxone, reduced primary and secondary hyperalgesia in a burn injury model. This is in agreement with results from previous studies (3) The response to a thermal injury seems to involve the endogenous opioid system

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A.587 Hemisensory impairment indicating thalamic dysfunction in patients with reflex sympathetic dystrophy

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Background and Goal of Study: Aim of this study was to evaluate the extent and quality of sensory impairment as well as other clinical features in patients suffering from Reflex Sympathetic Dystrophy (RSD)

Materials and Methods: A subtle neurological examination was performed independently by two examiners in 25 patients with chronic RSD

Results: Twenty one patients (84%) had sensory impairment attributable to RSD. In 8 patients (32%), sensory impairment was limited to the limb affected by RSD In 4 patients (16%) a sensory deficit in the upper quadrant of the body could be demonstrated. In addition, three of these patients had sensory impairment in the ipsilateral lower limb, unaffected by RSD.

In 9 patients (36%) with RSD, a hemisensory impairment could be observed which mainly affects temperature and pain sensation and was usually accompanied by allodynia in the affected limb. In six patients, allodynia was limited to the hand or foot. In others, it spreads over the whole limb and may even involve the upper or lower quadrant of the body

Conclusion: Pain seen in patients with chronic RSD might be a central pain. With respect to the hemisensory impairment we suppose that the thalamus plays a crucial role in the pathophysiology of chronic RSD. The part of the limb presenting with allodynia might be "overrepresented" in the processing of the ventral posterior nuclear group of the thalamus, whereas the remaining parts of the ipsilateral half of the body are "neglected" (1). Previously published findings (2) of unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain may support this hypothesis.

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A.588 Analgesic effect of adenosine on ischaemic pain in volunteers

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Background: Adenosine has been shown to have some analgesic action in animal experiments. ATP has been shown to have anaesthetic sparing effect in humans. This study was designed to establish whether adenosine has analgesic actions in man

Methods: Following local ethics committee approval and written informed consent eight ASA 1, male volunteers in a double blind placebo cross-over study received either an infusion of adenosine 100 μg/kg/min for ten minutes or saline placebo under CVS monitoring. One week later the study was repeated with the alternative infusion. The painful stimulus was tourniquet induced ischaemia in the exercising arm for the last 2 minutes of the infusion. Pain measurements were made before infusion, at the end of infusion and 15 mins, 1, 4 and 24 hours later. Pain was measured using 100 mm visual analogue scores (VAS). Statistical analysis was with Wilcoxon Matched Pairs Rank Sum test. The pain scores at the end of the infusions of adenosine and saline were compared in the same subject The sum of pain intensity difference (PID) in the 24 hours after infusion was also compared

Results: Pain measured by VAS was significantly reduced in the adenosine group as compared to the saline group at the end of the infusion (see Fig. 1). There were no significant CVS changes in either group. During adenosine infusion mild facial flushing and chest tightness were observed.

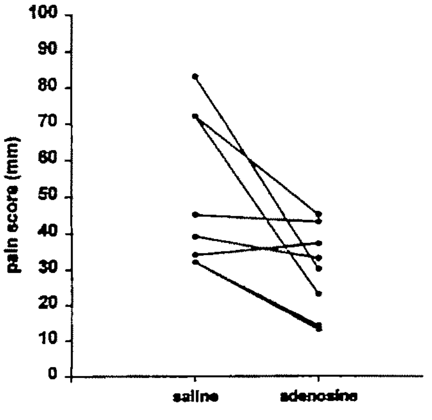

Fig 1 Pain Scores during Saline and Adenosine Infusions Median Difference 20 8 95% C I. 2.0–40.

Conclusions: Adenosine appears to have measurable effects on ischaemic pain but side effects may limit the clinical usefulness.

A.590 Intravenous testing of opioid sensibility in patients with chronic non-cancer pain and consecutive oral adjustment of pain medication

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Background and Goal of Study: An intravenous (iv) testing of pain sensibility with opioids (Morphine Test (MT)) is used to diversify an opioid sensitive versus a nonsensitive pain before starting a patient on opioid medication (1, 2, 3). So far, there is a lack of controlled trials which correlate the results of iv MT with the effectivity of an oral adjustment. In retrospective review of our own data only 72% of the patients responded to the oral adjustment in the same way as to the iv MT. Therefore, a randomised double-blinded trial has been started recently to investigate the sensibility and specitivity of the MT regarding pain sensibility to opioids and effectivity of the consecutive oral adjustment of opioid medication.

Material and Methods: After ethic committee approval, up to now 13 patients were randomised double-blinded to an iv morphine versus saline infusion at 2 different time intervals. Before, they had been documenting their pain intensity (VAS) and activity index (NAS) over 7 days. During time of infusion, pain intensity, respiration rate, width of pupils and side effects were noted every 15 minutes. All patients were then switched to an oral application of sustained released morphine at certain time intervals

Results: The infusion of saline did not lead to a significant reduction of pain in any patient 4 patients experienced a significant reduction of pain intensity ("responders") during the MT During consecutive oral adjustment with sustained released morphine 3 of 4 responders had again a decrease of pain. During investigation 9 patients showed no significant alteration in pain intensity at any time. Looking at the activity score, 2 responders had a marked increase. Some "non-responders" had a decrease of their activity index. In 1 responder medication had to be determined after developing edema of the thighs. All non-responders were discontinued for opioid medication. Typical side effects were observed more frequently in "non-responders" independently of route of administration

Conclusion: Preliminary results of the ongoing study demonstrate that all patients with a positive response to an iv MT also benefit from oral opioid application. Especially, no patient without pain reduction during the MT had a pain reduction during oral intake. This indicates that there is no false negative response for the iv MT

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A.591 Long-term oral opioid therapy in patients with non-cancer pain

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Background: There is considerable controversy about opioid therapy in patients with chronic non-cancer pain. The opponents argue that this therapy lacks of efficacy and leads to uncontrolled side effects Therefore we investigated all patients treated with opioids over a long period of time in our clinic.

Material and Methods: Data from 352 patients were evaluated retrospectively. 40 patients were treated ≥ 3 years. Pretreatment period, response to opioids, intensity of pain, measured by visual analogue scale (VAS), dosages of the opioids and side-effects were evaluated.

Results and Discussion: 15 males and 25 females were included. The duration of pretreatment lasted 10.6 years During the pretreatment period, patients had a total of 1242 regional blocks, 15 neurolytic blockades and 51 operations. The mean duration of opioid treatment was 4.9 years. 24 patients had pain relief of >50% (responder), 16 patients had a pain relief between 25–50% (partial responder) Pain decreased from VAS 8.6 before onset of treatment to VAS 3.9 during treatment. On the average, 273.7 mg slow release morphine/day (range: 30–990 mg) was used in 24 patients Buprenophine (n = 9) was used with a mean dosage of 2.61 mg/day (range: 0.6 to 4.6 mg), slow release DHC in 4 patients (average dosage: 307.5 mg/day, range: 120–720 mg) and slow release dextropropoxyphene in 3 patients (average dosage: 480 mg/day, range. 300–900 mg) Dosages were stable in 32 patients, increased in 3 and decreased in 3 patients. In 2 patients dosages were variable. Side-effects (sedation, vertigo, nausea, vomiting, pruritus) decreased, constipation increased during the long-term therapy.

Conclusion: If other therapies proved to be ineffective, controlled treatment of non-cancer pain with oral opioid analgesics may be a therapy with acceptable side effects and stable dosages

A.592 Electroacupuncuture for knee pain in elderly patients

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Background and Goal of Study: Acupuncture is one of the oldest types of pain treatment and it is known that it increases endorphins in various parts of the CNS [1] Electroacupuncture has been shown to provide analgesia through production of endorphins at 4 and 100 Hz[2] and serotonin at 200 Hz The goal of this study was to investigate the potentials and the efficacy of a combined treatment of auricular acupuncture and electroacupuncture in two frequencies in elderly patients with knee pain who had taken anti-inflammatory drugs (NSAIDs) in the past.

Materials and Methods: 92 elderly patients (>65 years) of the Pain Relief Unit complaining about knee pain were studied. They had been either unsuccessfully treated or they had stopped taking NSAIDs because of gastric bleeding or renal deterioration 2 patients, previously operated for total knee replacement were excluded from the study The present analgesic technique included a) a semi permanent needle at the knee point of the ear, inserted at the first day of treatment b) 7 courses of electroacupuncture in both knees at the acupunctural points S 34–36 or GB 33–34 on the lateral and SP 10 or L 7–8 on the medial aspects of the knee. No other medication was used The patients were assessed immediately after the treatment and once a month afterwards a) by our Knee Pain Scale including assessment of physical functioning, quality of night sleep, knee flexion, ability to walk without walking stick, performance in family surrounding b) by the patient's satisfaction and acceptance of the technique The duration of the analgesic effect was also documented

Results and Discussion: 90 patients, 26 male and 64 female were studied. Immediately after the courses 72 patients (80%) were clearly improved and very satisfied. Surprisingly, 15 patients were not improved but very satisfied by the technique. 3 posttraumatic patients were slightly improved during the acute phase The duration of the analgesic effect varied from 1 (67%) to 7 months (8%) No complications were reported.

Conclusion: Electroacupuncture combined with auricular acupuncture seems to be safe and effective in most elderly patients and provide an excellent alternative to NSAIDs treatment.

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A.593 Treatment of frozen shoulder with an interscalene block

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After mobilisation of a frozen shoulder, patients should work with a physiotherapist one to two times a day. In the remaining time patients have to exercise on their own; otherwise, the shoulder will loose mobility again. Exercise is only possible when the patients are free of pain during the exercises. Therefore adequate analgesic therapy for four to five days after the first mobilisation is of great importance. We treated patients suffering from a painful frozen shoulder with interscalene blockade of the brachial plexus for mobilisation. We investigated the efficacy of this technique by the registration of additional analgetics use and asking the patient's assessment The observation time was 18 months.

Methods: 37 patients were treated with an interscalene blockade (Winnie) of the brachial plexus using a catheter inserted at the affected side. Catheter location was verified with electric nerve stimulation. In all patients a bolus of 20 ml bupivacaine 0.375% was given for the first mobilisation, followed by 10 ml bupivacaine 0.25% every 6 hours

Results: In 34 of 37 (92%) patients mobilisation of the shoulder could superfound without general anaesthesia. 33 of 37 (89%) patients did not need any additional analgesics during the following mobilisations. The mean duration of catheter treatment was 4 days; infections occurred The following side effects were observed at the first mobilisation Horner syndrome in 20 patients (54%); paresis of the recurrens nerve in 9 patients (24%); paresis of the phrenic nerve in 6 patients (16%). During the consecutive treatment a Horner syndrome was visible in 15 patients (41%) and a paresis of the recurrens nerve in 8 patients (21%) In an interview after the end of the treatment period all patients stated that they would choose this method again, if necessary.

Conclusions: With the use of this regional anaesthesia technique it was possible to provide comfortable pain therapy during the mobilisation period. For a sufficient analgesia with only a mild motor blockade of the motoneurons the exact location of the catheter tip is important, which can be verified using electrical stimulation.

A.594 Intra-articular morphine: a relevant analgesic after day-case arthroscopy?

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Background and Goal of Study: Whilst intraarticular morphine (IAM) has been shown to have analgesic effect following arthroscopy (1), clinical benefit has not always been confirmed (2) This double-blind study aimed to determine whether a perioperative balanced analgesia regimen is enhanced by the addition of IAM

Materials and Methods: 100 day-case arthroscopy patients were randomised following anaesthesia (diclofenac/propofol/fentanyl/sevoflurane), to receive intraarticularly 20 ml 0 5% bupivacaine with or without 4 mg morphine (Gps: B + M and BUP) Patients assessed their pain by visual analogue scale (VAS 0 = no pain to max 10) at 2, 4, 6, 8, 12, 24, 48 h; recorded intake of rescue analgesic (paracetamol 500 mg + codein 30 mg) and occurrence of side-effects. Data was collected by telephone intervue on the 3rd day. VAS scores analysed by ANOVA, analgesic intake by Mann-Whitney U test.

Results and Discussion: Data was available from 95 patients, mean age 37 yrs range 16–68, 73% men, and 62% underwent interventional arthroscopy. Main results:

	Mean pain score (VAS 0–10)				Nil rescue analgesic % pat			Nausea % pat
	4 h	12 h	24 h	48 h	12 h	24 h	48 h	
BUP	2 1	2 7	1 7	1 6	43	43	40	9
B + M	2 0	2 0	1 8	1 4	39	36	36	39*

No significant differences except nausea * χ^2 P = 0 001

Median 3 tablets, range 1–11, were taken in both groups by those requiring rescue analgesic, intake was similar in the subsets gender and type of arthroscopy

Females had higher pain scores at all times and this was significant during the first 8 h (p = < 0.05). Interventional arthroscopy was associated with similar or lower pain scores compared to diagnostic (p = 0.05 at 6 &8 h) and a higher level of patient satisfaction, mean 9 vs 7 9, p = 0 01

Conclusion: In an arthroscopy population receiving balanced analgesia in the form of diclofenac, fentanyl and intraarticular bupivacaine, the addition of IAM did not result in superior or more long-lasting analgesia. This study also suggests that gender and case-mix are factors to be taken into account in pain perception measurement

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A.595 Efficacy of bupivacaine infiltration upon postoperative pain after ambulatory shoulder arthroscopy under general anaesthesia

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Background & Goal of the Study: Although intraarticular bupivacaine and/or morphine have demonstrated useful in some orthopedic procedures to lower postoperative pain (1, 2), the efficacy of local anesthetic infiltration in the subacromial space, which is not enclosed within a capsule (3), has not yet been proven The purpose of this study was to ascertain if bupivacaine infiltration after surgery would lower postoperative pain intensity and the request for analgesia in patients undergoing ambulatory shoulder arthroscopy under general anesthesia.

Material & Methods: Double blind, randomized, placebo-controlled prospective study in 40 patients. At the end of the surgery (subacromial decompression for subacromial impingement syndrome) and before closure of the portals, patients were injected with 30–40 ml of saline or 0.25% bupivacaine into the subacromial space Postoperative pain was measured using VAS (0–100 mm) at arrival in PACU, 30 minutes, 1, 2 hours and at hospital discharge Analgesic requirements of the patients in both groups were recorded Demographic data was compared using the t-test or rank sum test as appropriate Pain VAS scores and analgesic demands were analyzed by one-way ANOVA Results are expressed in mean ± SD

Results: Groups were similar with respect to age, weight duration of surgery and intraoperative dose of fentanyl. We found no differences on patients report of pain, time to first request for analgesic and total dose of postoperative analgesic, although mean VAS pain scores at 30 minutes were higher in the placebo group (5.9 ± 0.9) compared to the bupivacaine group (4 2 ± 2.6) (p = 0.08). No unplanned admissions and no significant differences in hospital stay were found between the two groups

Conclusions: The use of postoperatively bupivacaine infiltration into the subacromial space was not associated with reduced postoperative analgesia requirements and neither with a shorter hospital stay in ambulatory shoulder arthroscopy patients

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A.596 Intrapleural bupivacaine for prevention of pain after nephrectomy

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Controversial results (due to different techniques, dosages and different types of operations) have been published concerning the efficacy of post operative pain relief after ip (intrapleural) installation of local anesthetics The purpose of this study was to investigate whether ip 20 ml Bupivacaine 0 25%, every 6 hours, after nephrectomy will significantly reduce the need of post operative systemic opioids.

Methods and Patients: After informed consent and approval by the local ethic committee, 40 patients for elective nephrectomy were randomised into 2 groups At the end of the operation an ip catheter was placed medioaxillary at the 6th intercostal space in 22 patients and 20 ml Bupivacaine 0.25% was injected every 6 hours for 2 days, while 18 patients served as control

We compared the total amount of Piritramide needed postoperatively for the first 48 hours, and the time that elapsed after the insertion of the ip catheter until the first request for a systemic analgesic.

Analysis of variance and t-test (modified for samples with different variances) were performed to compare the total doses of Piritramide. T-test and Wilcoxon signed rank test were performed to compare the time until the first analgesic was asked for.

Results: There was no significant difference between the two groups concerning age, gender, duration of operation, type and duration of anesthesia. The total amount of Piritramide in the ip catheter group was significantly lower ($p < 0\ 01$) than in the control group on both days (23 mg ± 3.3 SE vs 45 mg ± 5.8 SE on the first day and 9 mg ± 2.5 SE vs 23 ± 3.7 SE on the second day) The time when the first analgesic was asked for was longer in the study group vs the control group (mean 5 h vs 2 h, median 3 5 h vs 1 h), but statistically significant only with the t-test ($p < 0\ 03$), while borderline ($p = 0.0609$) with the less powerful, but parameter free Wilcoxon signed rank test

Conclusion: 20 ml Bupivacaine 0.25% intrapleurally every 6 hours for two days reduces the need for systemic opiates for about 50% and may double the painfree time after nephrectomy The question now remains whether reducing systemic analgesia is an advantage for the patient and enough to recommend an invasive technique of analgesia such as the intrapleural installation of local anesthetics

A.597 Intraperitoneal bupivacaine injection and infusion via subphrenic catheter for postoperative pain management in laparoscopic cholecystectomy

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Laparoscopic cholecystectomy is frequently associated with less postoperative pain as compared with open cholecystectomy and causes three types of pain (visceral, parietal and shoulder pain). Laparoscopic pain is usually treated with i m or i.v. analgesic drugs, although some authors have used epidural analgesia or local anesthetic via subphrenic catheter (1, 2) The purpose of this prospective study was to evaluate the effect and the type of local analgesia via a subphrenic catheter compared to systemic analgesia on post operative pain scores.

Sixty patients (ASA grades I and II) who were undergoing elective cholecystectomy were studied after approval by the ethics committee. Local anesthetics or placebo solutions were given via a subphrenic catheter as follows bolus injection immediately after the creation of pneumoperitoneum (S1). bolus injection at the end of the operation (S2) and were infused after the operation during postoperative period for four hours (S3). Patients were randomly divided into four groups: **Group I** (control) received 20 ml of % 0.9 saline during S1, S2, S3. **Group II** (pre-cholecystectomy) received 20 ml of % 0.5 Bupivacaine during S1 and 20 ml of 0.9% saline during S2, S3. **Group III** (post-cholecystectomy) received 20 ml of 0.9% saline during S1, S3 and received 20 ml. of % 0.5 Bupivacaine only during S2. **Group IV** (infusion) received 20 ml of % 0.9 saline during S1, S2 and 20 ml of % 0.5, Bupivacaine infusion during S3. The degree of postoperative pain was assessed using visual analog scala (VAS-for visceral pain) and verbal rating scale (VRS-for parietal pain) scores on arrival in the recovery room just after surgery (T0) and at 1/2 h (T1), 1 h (T2), 2 h (T3), 4 h (T4) postoperatively. Consumption of analgesic agents (i.v. or i.m. meperidine when VAS score >4), the presence of shoulder pain, nausea and vomiting were recorded

Although VAS pain scores were less in all groups, it was only significant at T0, T1, T3 and T4 in Group IV when compared to the control group. However, no significant difference was observed in VRS scores between the groups. The least analgesic requirement occurred also in Group IV.

In conclusion, bupivacain infusion via subphrenic catheter effectively reduced visceral pain and the consumption of adjuvant opioid analgesia. In addition to the effective pain control, absence of side effects, easy and risk-free application make the infusion of local anesthesia via subphrenic catheter, a method of choice for post-operative pain in laparoscopic cholecystectomy patients.

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A.598 Randomized double-blind comparison of intravenous regional guanethidine with placebo in postoperative pain

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Introduction: The sympathetic nervous system has a role in pain transmission and modulation (1). Intravenous regional sympathetic blockade with guanethidine has been widely used in chronic pain management. This study aimed to investigate the effect of intravenous regional guanethidine on post-operative pain

Methods: After local ethical committee approval and written informed consent, 37 ASA I–II patients undergoing removal of orthopaedic prostheses from limbs were studied General anaesthesia was induced using propofol 2–2 5 mgkg^{-1} and fentanyl 1 mcgkg^{-1}, and maintained with patients breathing spontaneously isoflurane 1–2 5% and nitrous oxide 70% in oxygen via a laryngeal mask airway Following inflation of a pneumatic tourniquet on the operated limb, patients were randomised in a double-blind fashion to either receive intravenous guanethidine (10 mg for upper limb and 20 mg for lower limb) or placebo. Upon deflation of the tourniquet at the end of surgery, non-invasive blood pressure and pulse rate were recorded every minute for five minutes. Verbal numeric score for pain were obtained at 15, 30 and 60 minutes, and at 2, 4, 6 and 24 hours after arrival in recovery room. The amount of post-operative analgesics requested and the time to first dose of analgesic were noted. Overall patient satisfaction with pain relief was assessed using a five-point scale. Statistical analysis was performed with Chi-square, Student-t or Mann-Whitney U test, with $p < 0.05$ being significant.

Results & Discussion: 22 and 15 patients received IVR guanethidine and placebo respectively. There was no difference in age, site of surgery and tourniquet time Post-tourniquet deflation mean blood pressure and pulse rate, verbal numeric scores and patient satisfaction were similar between the two groups. Overall, 59% of patients did not request for any supplementary analgesic compared with 40% in the placebo group ($p = 0.25$). The time to first request for rescue analgesic was similar in both groups

Conclusion: IVR guanethidine does not have any clinical advantage in acute pain relief after removal of orthopeadic implants, although the amount of postoperative analgesic consumption appeared to be lower

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A.599 Clonidine does not affect postoperative pain when given as the sole analgesic agent into the axillary brachial plexus sheath

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Introduction: Clonidine (C) increased the duration of analgesia after axillary brachial plexus block when mixed with local anesthetic.[1] However the efficacy of C as sole analgesic has not been evaluated This study was conducted to determine if C has analgesic effects on its own when administered into brachial plexus sheath

Materials & Methods: 30 patients scheduled for hand surgery, were randomly divided into 3 groups of 10. Axillary brachial plexus block was performed with lidocaine and a catheter was inserted into the neurovascular sheath. At the end of surgery, considered as baseline, patients received through the catheter 15 ml of saline (group I), 150 μg of C in 15 ml of saline (group II) or 15 ml of 0.25% bupivacaine (group III). Postoperative pain on a visual analog scale (VAS) was checked every 2 hours until the end of the study period (6 hours). Ketorolac tromethamine 30 mg i.m was given on request Time from baseline to onset of pain and total dose of ketorolac were recorded. Side effects were also evaluated. Data were analysed using analysis of variance, Student-Newman-Keuls-, Kruskal-Wallis- and chi-squared test as required

Results: Demographics, type and duration of surgery were not significantly different between the groups There were no differences between group I and group II in time to onset of pain (72 ± 30 vs 68 ± 28 min), dose of ketorolac (45 ± 15 vs 42 ± 15 mg) and VAS scores during the study period Bupivacaine produced a significant prolongation of postoperative pain free period (260 ± 84 min; P < 0.001 vs groups I and II) and a reduction in total dose of ketorolac (42 ± 15 mg; P < 0.001 vs groups I and II) VAS scores were lower in group III than in the other groups at 2 (P < 0.001) and 4 (P < 0.05) hours. Two patients in group II had clinically relevant hypotension and one bradycardia

Conclusions: Although several "in vitro" lines of evidence[2, 3] support an intrinsic analgesic effect of C, we conclude that administration of 150 μg of C into the axillary brachial plexus sheath at the end of surgery does not produce postoperative analgesia

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A.600 Postoperative analgesia after ankle block: lidocaine plus clonidine. A dose-ranging study

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Background & Goal of Study: Addition of clonidine (C) to local anaesthetics prolonged pain relief after nerve block[1]. The aim of this study was to define a dose-response relationship for C added to lidocaine for ankle block.

Materials & Methods: 80 patients undergoing foot surgery were randomized to receive ankle block with 15 ml of plain 1 5% lidocaine (Group I; n = 20), 1.5% lidocaine with 37.5 μg C (Group II, n = 20), 1.5% lidocaine with 75 μg C (Group III; n = 20) or 1.5% lidocaine with 150 μg C (Group IV, n = 20). Time from the performance of the block to onset of postoperative pain and to first pain medication request were recorded. Ketorolac tromethamine 30 mg i.m. were given on request. Level of pain was evaluated on visual analog scale (VAS) 3, 6 and 9 hours after the block Total amount of ketorolac required during the study period (9 h) was recorded Side effects were also evaluated. Analisys of variance, Student-Newman-Keuls-, Kruskal-Wallis and Mann-Whitney U test were used as appropriate. Data are expressed as mean ± DS.

For statistical significance see text

	Group I	Group II	Group III	Group IV
Onset of pain (min)	162 ± 47	236 ± 49	274 ± 57	345 ± 50
Time to first analgesic	201 ± 54	279 ± 51	327 ± 66	395 ± 52
Dose of ketorolac (mg)	52 ± 16	40 ± 17	39 ± 17	34 ± 14
VAS 3 h	3 ± 1 9	1 1 ± 1 2	0 5 ± 0 7	0 2 ± 0 3
VAS 6 h	4 2 ± 1 1	3 7 ± 1 6	3 3 ± 1 5	1 9 ± 1.2
VAS 9 h	3 3 ± 1 0	3 1 ± 1.0	2 8 ± 1.0	2.5 ± 1 1

Results: (see table 1) time to report of first pain and to first analgesic request were significantly different between all groups (II vs III· P < 0.05; P < 0.001 in the remaining cases). There was a significant difference with regard to the dose of ketorolac (I vs IV· P < 0 001, I vs II and III: P < 0.05) and the VAS score at 3 h (I vs II, III and IV: p < 0.001, II vs IV P < 0.01), 6 h (IV vs I and II: P < 0.001; IV vs III: P < 0.005) and 9 h (I vs IV: P < 0.05). No clinically relevant side effects were recorded.

Conclusions: addition of C prolongs the duration of analgesia after ankle block. Unlike other similar studies[2], our results argue for a dose-dependent effect. An increased dose was not accompanied by a greater number of adverse side effects

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A.601 Postoperative analgesia by continuous epidural infusion of bupivacaine after repairing herniated lumbar disk

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Background and Goals of Study: The objective of this study was to determine the efficiency of the use of low bupivacaine doses in continuous epidural infusion for pain treatment, in the first 24 hours of the postoperative period, after lumbar laminectomy.

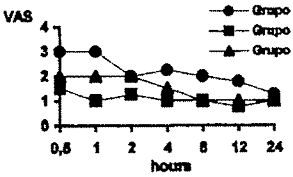
Materials & Methods: A randomized double-blind study was carried out on 27 patients, undergoing elective lumbar discectomy The patients were allocated to one of the following groups Group 1 (n = 8), 0 0625% bupivacaine infusion at 1.5 mg.h^{-1}; Group 2 (n = 10), 0.125% bupivacaine infusion at 3 mg h^{-1}, Group 3 (n = 9), 0 250% bupivacaine infusion at 6 mg.h^{-1}. Before the closure of the surgical incision, the surgeon placed, under direct vision, a catheter in the epidural space in the middle of the surgical field In the moment of the closure of the skin, a bolus of 4 ml of the anaesthetic solution was administrated through the epidural catheter, followed by an infusion of the same solution at 2 4 ml h^{-1}. The supplementary analgesia was provided by a system of ketorolac PCA at 10 mg per demand dose, with a lock-out interval of 5 min and a maximum dose of 30 mg in 4 h In those cases of VAS superior to 3 and maximum ketorolac dose, we used, as rescue analgesic, an IV bolus of meperidine (20 mg). The ketorolac doses during the period of study were registered The VAS, VRS, and side effects were evaluated. The VRS recorded during 24-h period was summed to yield the total pain relief (TOTPAR) score Statistical analysis included Kuskal-Wallis, Mann-Whitney and Friedman test

Results: The three groups were similar respect to age, gender, body size, amount of fentanyl used intraoperatively, and duration of surgery. No patient developed infection at the catheter site. The consumption of analgesics and TOTPAR score are reflected in following table

	Group 1	Group 2	Group 3
Ketarolac (mg)			
Total (24 h)	120 (80–180)*	30 (0–50)	30 (20–60)
0–8 h	60 (60–60)*	20 (0–40)	30 (10–40)
8–16 h	30 (0–60)*	5 (0–20)	0 (0 –20)
16–24 h	30 (20–60)*	0 (0–10)	0 (0–10)
Meperidine i v (mg)	20 (0–60)*	0 (0–0)	0 (0–0)
TOTPAR	17 5 (12–19)*	20 5 (17–21)	19 (15–21)

Values are median (range) * Significantly different from Groups 2 and 3 ($P < 0$ 05)

The postoperative pain scores were lower in Groups 2 and 3 as compared to Group 1 (figure)



Conclusions: We conclude that the continuous epidural infusion of 0 125% or 0 250% bupivacaine is an easy and effective technique in the management of pain after lumbar laminectomy. However, we observe a greater incidence of adverse effects (numbness, need for urinary catheterization) in those patients treated with 0.250% bupivacaine

A.602 Continuous epidural analgesia with morphine and ketamine for postoperative pain relief

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Background & Goal of Study: The epidural administration of opioids provides effective analgesia with side effects of nausea, vomiting, pruritus and sedation. Ketamine, an N-methyl-D-aspartic acid receptor antagonist, has been shown to produce postoperative pain relief administrated epidurally (1, 2) The goal of this study was to compare the analgesic and side effects of continous epidural analgesia with morphine alone and morphine plus ketamine during the first 24 h after elective lower abdominal surgery

Material & Methods: Forty-six ASA 1–2 patients were randomly assigned into two equal groups. Group I received a bolus of 3 mg epidural morphine in 10 ml saline before the end of surgery, followed by a continous infusion at a rate of 0 1–0 3 mg/h Group II received a bolus of 3 mg morphine and 10 mg ketamine in 10 ml saline administered epidurally, followed by continous infusion of morphine at a rate of 0.14–0.28 mg/h and ketamine at a rate of 0.4–0.8 mg/h All patients were observed for pain relief and adverse effects for 24 h. Pain was assessed using linear analogue scale from 0–10.

Results & Discussion: Mean morphine consumption was 9.5 ± 0.4 mg for Group I and 6.8 ± 0 2 mg for Group II. Pain relief was better in Group II than in Group I ($p < 0.05$), despite Group II utilized significantly less morphine ($p < 0.05$) Vomiting occurred more frequently in Group I (30%) than in Group II (14%) The frequency and severity of pruritus and sedative levels were similar in the two groups

Conclusion: Continous epidural analgesia with morphine plus ketamine decreases morphine consumption, provides better pain relief and less adverse effects than continous epidural analgesia with morphine alone. So, this method is an acceptable alternative to continous epidural analgesia with morphine alone after low abdominal surgery

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A.603 Caudal clonidine for postoperative analgesia in adults

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Background and Goal of Study: Caudal block can be used in adults for sacro-perineal surgery (1). This prospective, double-blind, randomized, placebo controlled study was designed to assess the efficacy of caudally administered clonidine in adults when added to local anesthetics

Materials and Methods: After IRB approval, 58 ASA I–II patients scheduled to undergo haemorrhoidectomy were included in the study. Patients were randomly allocated to one of two groups. All received a caudal injection of a mixture containing 0.5% isobaric bupivacaine 35 mg in 2% lignocaine 140 mg with epinephrine 1/200000; In addition, patients were given clonidine 75 μg (group C) or saline 1 ml (group S). Postoperative followup was performed by a blinded observer. Duration of analgesia defined as the time from the caudal injection to the first request for supplemental analgesics was recorded For patients not requiring analgesics during 48 hr, duration of analgesia was defined as 2880 min

Analysis of variance (ANOVA) was used for Intergroup comparison and Fisher's Exact Test for categorical data. Results are expressed as mean ± SD Statistical significance was considered at $P < 0.05$.

Results and Discussion: Demographic data were comparable between groups. Bradycardia was significantly more frequent in the group C compared to the group S ($p = 0.01$) but without significant changes in Mean Arterial Pressure No significant differences were found between groups for other side effects The median time to first analgesic request was significantly longer in group C (729 ± 120 min) than in group S (276 ± 131 min) ($P = 0.01$).

The main side effects of extradurally administered clonidine are hypotension, bradycardia and sedation (2) Hypotension was not marked in our study. Bradycardia was more frequent in the clonidine group but had no hemodynamic repercussion. Clonidine produces dose-dependent sedation (3) Postoperative sedation in our study was similar in both groups This could be explained by the low dose of clonidine used

Conclusion: Clonidine may be a potentially useful drug when prolonged postoperative analgesia is required after caudal block in adults.

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A.604 Continuous spinal anaesthesia or continuous epidural anaesthesia for postoperative pain control after hip replacement?

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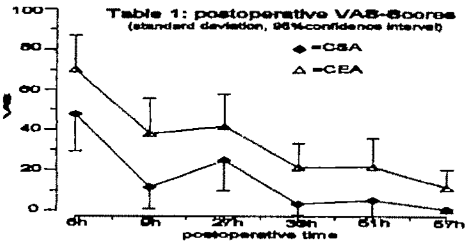
Background & Goal of Study: Both continuous spinal anaesthesia (CSA) and continuous epidural anaesthesia (CEA) are supposed to provide adequate postoperative pain relief. The purpose of this randomized, prospective study was to compare quality of analgesia, occurrence of side effects and patients' satisfaction between spinal and epidural administration of bupivacaine 0.25% during the first postoperative 72 hours.

Materials & Methods: Following approval of the Ethics Committee, 102 patients scheduled for hip replacement (65 f, 37 m) were randomly assigned to one of 2 groups: Group 1 ($n = 51$) received CSA for intraoperative and postoperative management, Group 2 ($n = 51$) received CEA. Right after surgery, the CSA-Group received a 1 ml bolus (bv 0.25%), followed by continuous Infusion of 10 ml/24 h. The CEA-Group received a 10 ml bolus, followed by 2 ml/h. The level of pain was gauged from verbal rating scale (VRS) 6 hours after the first bolus in the Intensive Care Unit and from visual analogue scale (VAS) twice a day, the degree of motor blockade was registered with Bromage score. For statistical analysis, Wilcoxon two sample test and Chi-square test were used.



Results & Discussion: No difference in demographics was noted 90.2% of the CSA-Group, but only 21.6% of the CEA-Group reported complete analgesia on the VRS The VAS-scores given by the CSA-Group were significantly lower than those of the CEA-Group (figure)

The percentage of patients with a motor block decreased within the first 24 hours from 39.2% to 5.88% in the CSA-Group and from 9.8% to 0% in the CEA-Group The satisfaction was considered excellent in 92.2% of the CSA-Group and in 70.6% of the CEA-Group During the first 24 hours, nausea and vomiting occurred significantly more often in the CEA-Group No neurological impairment arose

Conclusion: CSA and CEA are effective and safe for postoperative pain relief after hip replacement Compared to CEA, CSA provides faster onset of pain relief, ensures better analgesia and results in more satisfied patients

A.605 Comparison of epidural and intravenous sufentanil patient-controlled analgesia combined with epidural bupivacaine

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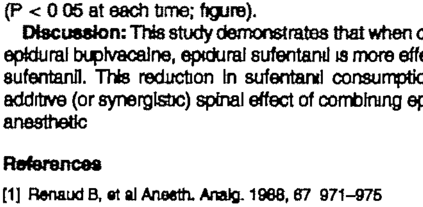
Introduction: The risk of respiratory depression may be less with epidural lipophilic opioid than with epidural morphine [1] However, controversy over the mechanism(s) of action of epidural sufentanil (spinal vs systemic action) persists [2, 3] All previous studies compared epidural to intravenous sufentanil alone. Clinical practice usually involves use of local anaesthetics and opioid, to benefit from a possible additive or synergistic effect of their combination. We therefore compared epidural and intravenous sufentanil combined with epidural bupivacaine (BUPI) to relieve postoperative pain after major abdominal surgery.

Methods: After IRB approval, 40 ASA II–III patients were included in this randomized study Patients had surgery with general anaesthesia (isoflurane) and thoracic (T8–T11) epidural anaesthesia (6–8 ml) of BUPI 0.5% followed by a continuous infusion (6–8 ml/h) of BUPI 0.25%. On arrival in the PACU, patients were randomly allocated to receive a continuous infusion (5 ml/h) of BUPI 0.1% and epidural sufentanil (EPISUF) or the same epidural infusion of BUPI combined with intravenous sufentanil (IVSUF). Sufentanil in the two groups was administered using the same PCA pump and the same settings: bolus = 2.5 μg, lockout interval = 10 min. An investigator blinded to patient allocation group recorded the following parameters 4 h after the end of surgery, at 9.00, 14.00 and 19:00 on days 1 and 2: pain (100 mm VAS) at rest, during mobilization, and coughing, and the dermatomal extension of epidural analgesia Sufentanil consumption was also recorded every 4 h. Data (mean ± SEM) were analyzed by ANOVA.



Results: Patients characteristics were similar in the 2 groups. Pain relief at rest, during mobilization and coughing as well as extension of epidural analgesia were not significantly different in the two groups. Sufentanil consumption was 50% less in the EPISUF group than in the IVSUF group ($P < 0.05$ at each time; figure).

Discussion: This study demonstrates that when combined with low dose epidural bupivacaine, epidural sufentanil is more effective than intravenous sufentanil. This reduction in sufentanil consumption may result from an additive (or synergistic) spinal effect of combining epidural opioid with local anesthetic

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A.606 Propofol *vs* naloxone: effect and adverse effect on epidural morphine-induced pruritus

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Background & Goal of Study: Pruritus is the most frequent undesirable symptom associated with epidural morphine. It is unpleasant and often difficult to treat. Naloxone is presently the drug of first choice for treating this symptom. However naloxone decrease the pain threshold in some cases. Recently it was reported that subhypnotic doses of propofol were efficient in relieving epidural-morphine induced pruritus (EMIP)[1]. In a prospective, randomized, double-blinded clinical trial, we compared the efficacy of propofol and naloxone for the treatment.

Materials & Methods: After obtaining informed consents from patients and with IRB approval, 92 patients having cesarean section, received epidural morphine 3 mg bolus, and 4 mg/day with continuous infusion for 2 days via Baxter infusor®. The patients who have pruritus with scratching were allocated to received either 20 mg propofol or 1.5 μg/kg naloxone intravenously. Pruritus and the level of postoperative pain were assessed 5 minutes later using 5 points pruritus rating scale (PRS) and 10 points visual analogue pain scale. Statistical analysis was performed using chi-square test and paired t-test. $P < 0.05$ was considered significant.

Results & Discussion: Sixty patients showed pruritus with scratching ($PRS \geq 3$). The overall success rate in treating pruritus was similar in two groups (propofol 73% vs naloxone 70%). Twenty-seven percent of the patients in the naloxone group had an increase in the level of postoperative pain versus none in the propofol group ($p = 0.018$). The beneficial effect of treatment was longer than 60 minutes in both groups.

	Propofol (n = 30)	Naloxone (n = 30)
Success rate	22 (73%)	21 (70%)
Change of VAS > 2	0 (0%)	8 (27%)*
Duration of effect (min)	176.9 ± 144.6	144.2 ± 152.5

Values are mean ± SD. *$p < 0.05$, VAS: 10 points visual analogue pain scale

Conclusion: These results suggest that 20 mg propofol and 1.5 μg/kg naloxone are equally effective in treating EMIP. However, the level of postoperative pain is significantly less in the propofol group than naloxone group.

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A.607 What is the minimum effective dose of propofol in relieving epidural-morphine induced pruritus?

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Background & Goal of Study: Pruritus due to spinal morphine has been thought a facilitatory action of morphine on nonnociceptive neurons in the posterior horn. Mu-receptor antagonists are considered effective for the treatment of epidural-morphine induced pruritus (EMIP)[1]. However, they have been associated in certain cases with concomitant reduction in analgesia. It is noteworthy that propofol has been shown to produce marked spinal depression, in particular of the dorsal and ventral horn. Recently it was reported that subhypnotic doses of propofol were efficient in relieving EMIP. This study was designed to investigate an effective minimal dose of propofol.

Materials & Methods: After obtaining informed consents from patients and with IRB approval, 155 patients having cesarean section, received epidural morphine 3 mg bolus, and 4 mg/day with continuous infusion for 2 days via Baxter infusor®. The patients who have pruritus with scratching were allocated randomly to one of the three groups. Patients received 10 mg propofol intravenously in group I ($n = 25$), 20 mg in group II ($n = 25$) and 30 mg in group III ($n = 25$). Pruritus and the level of sedation were assessed 5 minutes later using 5 points pruritus rating scale (PRS) and 4 points sedation rating scale (SRS). Statistical analysis was performed using chi-square test, one-way ANOVA and paired t-test. $P < 0.05$ was considered significant.

Results & Discussion: Seventy-five patients showed pruritus with scratching ($PRS \geq 3$). The success rate was significantly greater in the group II (76%) and group III (80%) than in the group I (48%) ($p < 0.05$). Seven patients had an increase in sedation in the group III versus none in the group I and group II ($p < 0.05$). The beneficial effect of treatment was longer than 60 minutes in 100% of patients in group I, II and III.

Propofol	10 mg	20 mg	30 mg
Success rate	48%	76%*	80%*
Sedation rate	0%	0%	28%**
Duration of effect (min)	226.8 ± 162.7	222.4 ± 105.7	235.8 ± 141.2

Values are mean ± SD. *$p < 0.05$ versus 10 mg propofol group, **$p < 0.05$ versus 10 mg and 20 mg propofol proup

Conclusion: These results suggest that 20 mg propofol and 30 mg propofol intravenously are equally effective in treating EMIP than 10 mg propofol. However the level of sedation is significantly less in 20 mg propofol group than 30 mg propofol group.

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A.608 Incisional morphine has no analgesic effect after inguinal herniotomy

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Background and Goal of Study: Opioids induce antinociceptive effects after peripheral administration in experimental and clinical studies (1–2). The results of the clinical studies are conflicting (2–3). The objective of this study was to examine the possible effect of incisionally administered morphine on postoperative pain in patients undergoing inguinal herniotomy under general anaesthesia.

Materials and Methods: A total of 46 consecutive outpatients were included in a double-blind randomized, placebo-controlled study. At conclusion of herniotomy morphine was injected incisionally in 11 patients, intravenously in 10, and subcutaneously in 13. The placebo group of 12 had saline injected in the incision. Postoperative pain at rest and during mobilization was assessed with a visual analogue scale. Assessments were made immediately before and after herniotomy, at 2, 4, and 6 hours after surgery, and on the second and seventh postoperative day. Postoperative morphine and acetaminophen consumptions were recorded within the same period.

Results and Discussion: There were no significant differences in visual analogue scores between the groups at any time during the study. Overall differences in postoperative acetaminophen and morphine consumptions were insignificant.

Most studies finding an analgesic effect after peripheral administration of morphine have included patients undergoing arthroscopic knee surgery (2). Inguinal herniotomy is probably a more extensive surgical trauma compared with arthroscopy of the knee and, therefore, may cause more postoperative inflammation and more pain. The morphine dose in this study may have been too small as compared to the intensity of inflammation.

It is not known at what time after incision opioid receptors appear at the nerve endings. If none or very few opioid binding sites are present peroperatively, it is unlikely that incisionally administered morphine can produce an early pain relieving effect. Moreover the likelihood that any morphine is left to interact with newly produced opioid receptors in the wound several days after injection is probably very small.

Conclusions: The analgesic effect of a single 5 mg dose of morphine injected in a herniotomy wound is not superior to saline or to morphine given subcutaneously or intravenously.

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A.609 Morphine titration in PACU. Comparison of two time intervals between bolus: 10 *vs* 5 min.

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Background: The goal of morphine titration is to rapidly relieve pain in acute care. Using this concept for postoperative pain management, we have implemented a continuous quality assurance program in the post anaesthesia care unit (PACU). According to analgesic efficacy and side effects, we have compared the interval between two morphine bolus: 10 min and 5 min.

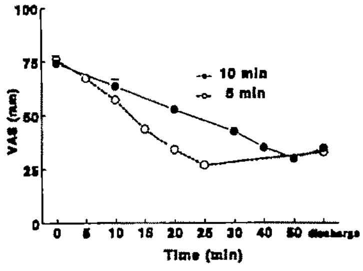
Patients and Methods: The patients were queried about the presence of pain and asked the rate pain intensity on a 100 mm visual analog scale (VAS). In the first period (400 patients), when pain increased to more than 30 mm, (VAS control) iv morphine was titrated up to 15 mg *every 10 min* by 3 mg increments (10 mg by 2 mg increments if weight < 60 kg). In the second period (400 patients), iv morphine was titrated *every 5 min*. A VAS reduction to less than 30 mm or major side effects (sedation, respiratory rate <10/min) lead to stop the morphine titration. Values are mean ± SEM.

Results and Discussion: There were no significant differences in analgesic scores and side effects at the end of titration (VAS 1) or on discharge (VAS 2) of the PACU, between the two groups (table 1). Sedation was

	Group 10 min	Group 5 min
VAS control mm	74 ± 4	76 ± 1
VAS (1) mm	30 ± 1	27 ± 2
VAS (2) mm	34 ± 1	33 ± 1
Side effects n (%)	40 (10)	28 (7)
Sedation n (%)	106 (27)	144 (36)*

* $p < 0.01$ vs 10 min

however more pronounced in group 5 min. The mean dose of morphine was 9 6 mg and was not influenced by the interval between bolus. Pain was more rapidly relieved in the group 5 min (figure 1)



Conclusion: The major finding of this study was the most rapid analgesic effectiveness of morphine bolus injected every 5 min without significant increase in side effects incidence

A.610 Analgesia and respiratory depression time course during morphine loading dose in recovery room

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Background: After major surgery, a loading dose of intravenous morphine given in a recovery room is a useful starter to postoperative analgesia. The criteria of administration and duration of patients monitoring in recovery room are still debated. The goal of this study was to assess the time course analgesia and respiratory side effects during and after this loading dose.

Methods: Pain was assessed every 10–15 minutes using a simplified verbal score, SVS (from 0 = no pain to 5 = intolerable pain). The loading dose of morphine was given as follows: a bolus of 5 mg intravenously, then 3 mg every 10 minutes until the SVS was under 2 (2 = moderate pain) with no maximal dose.

Respiratory side effects were detected by $SpO_2 < 93\%$ or respiratory rate < 8/min.

Results are expressed as mean (min, max). Comparison were performed by t paired test Differences yielding $p < 0.05$ was considered significant

Results: Over a 3 months period, 27 consecutive patients were included. The total loading dose of morphine was 24 mg (8; 47). The simplified verbal score was 2 (2; 4) at the end of loading dose. In 5 patients loading dose was stopped before the criteria because of respiratory depression After loading dose, analgesia continued to improve, achieving a minimal simplified verbal score of 1 ($p < 0.05$), after an average delay of 40 min (10; 100)

Respiratory depression occurred in 13 patients (in 5 patients before the end of morphine loading dose, in 3 patients following the last bolus at 10 min and 60 min and in 5 patients the loading dose was stopped because of low respiratory rate).

Discussion: After intravenous morphine loading dose the maximal effects may be delayed regarding analgesia as regarding respiratory side effects. This suggests that the criteria for stopping morphine loading dose should be moderate pain rather than light or no pain and could be enraced by non opioid analgesics. Prolonged monitoring in recovery room (>1 hour after the last bolus) is always necessary.

A.611 Effects of morphine and oxycodone on respiration and haemodynamics

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Background: Thorough understanding of the respiratory and haemodynamic effects of morphine and oxycodone is necessary for their optimal use. These effects were studied on healthy volunteers under experimental pain stimulation.

Methods: 8 healthy male volunteers were studied in a random, double-blind and cross-over fashion. Pain was induced with a 300 mmHg tourniquet. After 4 minutes the subjects were given either morphine 0.14 mg/kg (M1), morphine 0.07 mg/kg (M2), oxycodone 0 14 mg/kg (O) or placebo (P) as a 2 minutes injection. The tourniquet was kept on for a total of 10 minutes (4 minutes post drug injection). Radial artery was cannulated for measurements of heart rate (HR), mean arterial pressure (MAP) and for sampling of blood gases (PaO_2 and $PaCO_2$), catecholamines and histamine. Oxygen saturation (SPO_2) was measured with a pulseoximeter. Respiratory inductive plethysmograph was used to measure minute ventilation (VE). Measurements of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were performed with a indirect calorimetry. Alveolar ventilation (VA) was calculated from formula $VA = 0.115 \times VCO_2/PCO_2$. Data sampling was done at baseline (bl), during pain stimulation (ps), right after drug injection (0), 4 minutes after drug injection (before releasing the tourniquet) (4) and 10, 15, 20 and 30 minutes after drug injection. ANOVA was used for data analysis and $p < 0\ 05$ was considered significant.

Results: P had no effect on measured parameters. Both M1 and M2 induced an immediate, but transient increase in MAP and HR ($p < 0\ 05$). No such effect was seen after O treatment Compared to P, all active drugs decreased VE ($p < 0\ 05$), with no difference between O, M1 or M2. However, VA decreased significantly more after O than after either of the M doses. This was also reflected in $PaCO_2$-values, which were significantly higher after O than after either M1 or M2. PaO_2 was lower than P only after O ($p < 0\ 05$). The changes in respiratory parameters were clinically insignificant, and quite similar after both M1 and M2

Conclusions: The difference in respiratory effects between oxycodone and both morphine doses is best explained by dosage; the potency ratio of 1:1 between oxycodone and morphine probably underestimates the potency of oxycodone However, the dosage cannot explain the difference in haemodynamic response, as cardiovascular stimulation was evident and similar for both morphine doses.

A.612 Control of immediate postoperative pain in patients who received remifentanil during balanced anaesthesia for moderately painful surgery

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Background: Remifentanil is a new μ-opioid agonist with an ultra-rapid elimination which implies an anticipation of postoperative pain by an analgesic treatment administered before remifentanil infusion is ended The objective of this prospective, double-blind, randomised study was to evaluate the efficacy and safety of propacetamol 2 g (P) associated with ketoprofene 100 mg (K) or nalbuphine 20 mg (N) in managing early postoperative pain.

Methods: 235 patients aged 18 to 65 years old, ASA status I–II, requiring a laparoscopic surgery (cholecystectomy, gynaecological surgery) with a planned duration of 45 min to 2 hours and receiving remifentanil during balanced anaesthesia were included into the study. They were randomized to receive, 30 minutes before the end of remifentanil infusion, either P and K or P and N (after the end of remifentanil infusion). Postoperative pain was evaluated during the first 15 minutes by behavioural score (BS graded from 1 to 3), and until discharge from recovery room by a simple verbal scale (SVS graded from 0 to 3). In case of postoperative pain, an analgesic rescue medication was administered to the patient

Results:

Group	PK (n = 120)	PN (n = 115)	p
Time to first rescue analgesic.			
median	37.5 min	32 min	NS
For the first 15 min after the end of remifentanil infusion			
BS < 2 (% patients)	80	74	NS
15 to 30 minutes after the end of remifentanil infusion·			
SVS < 2 (% patients)	56	50	NS
Administration of rescue analgesic 1 hour after the end of remifentanil infusion·			
(% patients)	47	46	NS

No serious adverse events have been reported in this study

Conclusion: In moderately painful surgery, the 2 combinations (propacetamol-ketoprofene or propacetamol-nalbuphine) in this study have a similar efficacy and were well tolerated. These 2 combinations provide a satisfactory analgesia during the immediate post operative period which allows a transition to other analgesia under the best conditions.

A.613 Control of immediate postoperative pain in patients who received remifentanil during balanced anaesthesia for severely painful surgery

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Background: Remifentanil is a potent and selective μ-opioid agonist with an ultra-rapid elimination which implies an anticipation of postoperative pain by an analgesic treatment administered before remifentanil infusion is ended. The objective of this study was to evaluate the efficacy and safety of 2 dosages of iv morphine in managing immediate postoperative pain.

Methods: Adult patients, ASA status I–III, requiring a major abdominal or uro-genital surgery under laparotomy and receiving remifentanil during balanced anaesthesia were included into the study. They were randomized to receive iv morphine either 0.15 mg/kg or 0 25 mg/kg administered 30 minutes before the end of remifentanil infusion.

Postoperative pain was evaluated during the first 15 minutes by behavioural score (BS 1 to 3 graded), and until discharge of recovery room by a simple verbal scale (SVS 0 to 3 graded). In case of postoperative pain, a titration of morphine was performed until pain relief.

Results: 245 patients received the randomized study treatment. For the first 15 min after the end of remifentanil infusion:

Group.	0 15 mg/kg n = 121	0 25 mg/kg n= 124	p*
BS < 2 (% patients)	65	79	0.026

Between 15 and 30 min after the end of remifentanil infusion:

Group	0 15 mg/kg	0.25 mg/kg	p*
SVS < 2 (% patients)	30	41	0 030

*p level of significance <0 05

The percentage of adverse events was similar in the 2 groups; nevertheless, in the postoperative period, three respiratory depressions, two of which were late, occurred in the 0.25 mg/kg morphine group, with complete resolution for all three.

Conclusion: Although a number of patients experienced moderate or severe postoperative pain during the first 15 minutes after the end of remifentanil infusion, the majority of patients reported no noticeable pain during this period. The higher dose of morphine provided better pain control but cannot be recommended because of the respiratory depressions. Complementary studies should investigate optimising postoperative pain control following the use of remifentanil in severely painful surgery.

A.614 Morphine before the termination of remifentanil provides effective transition to routine analgesia after major surgery: a comparison with current practice

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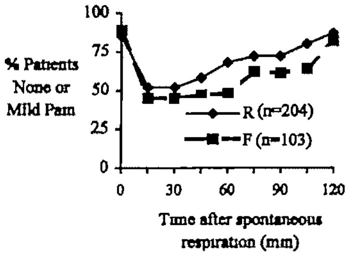
Background and Goal of Study: Remifentanil (R) is a potent μ-opioid agonist with a rapid onset and offset of action Measures should therefore be taken to prevent postoperative pain before R is discontinued. We compared postoperative pain control and recovery profiles when morphine (M) is given before the termination of R with routine pain management following fentanyl (F).

Materials and Methods: 316 male and female, ASA status I–III, patients (aged 18–75 years) scheduled for major abdominal, breast, gynaecological or orthopaedic surgery ($\geq$ 60 min duration) were recruited into this open study. 307 patients were included in the efficacy analysis. Patients were randomised 2:1 to receive either R (1.0 μg/kg then 0.5 μg/kg/min–0.25 μg/kg/min) or F (3.0 μg/kg then 1 5–3 μg/kg as required) Anaesthesia was induced with propofol and maintained with isoflurane (0.8% and 0 6% end tidal with F and R respectively). Thirty minutes before the anticipated end of surgery R patients received M (0 2 mg/kg) Postoperative pain was managed in both groups with M: 2.5–5.0 mg bolus doses as required followed by patient controlled analgesia (PCA) when pain control was considered satisfactory. Pain scores (none, mild, moderate, severe) and sedation scores (awake, drowsy, very drowsy, unrousable) were recorded every 15 minutes until discharge to the ward.

Results and Discussion: Intraoperatively R patients had fewer interventions. R patients were more likely to have no or mild pain 30–120 min after spontaneous respiration (Fig) (odds ratio >1). Over 50% of R patients required no additional M prior to PCA.



F patients received the last bolus dose 100 ± 43 min before the cessation of isoflurane. Therefore mean times to spontaneous and adequate respiration, and extubation were all significantly ($p < 0.05$) shorter in F patients (3.9 ± 3.7 vs 6 7 ± 3 8 min; 5.6 ± 5.1 vs 8.0 ± 4.3 min; 8 2 ± 6.0 vs 8 8 ± 4.6 min). These differences are clinically unimportant. R patients were more likely to be classified as 'awake' 0–45 minutes after spontaneous respiration (odds ratio >1).

Conclusion: In the transition to routine analgesia, M (0 2 mg/kg) given 30 minutes before the termination of R does not compromise recovery and provides a similar level of pain control to that provided by current practice following F.

Acknowledgements: This study was sponsored by Glaxo Wellcome UK

A.615 Postoperative pain management and recovery after remifentanil-based anaesthesia with isoflurane or propofol for major abdominal surgery

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Background and Goals of Study: Remifentanil (R) is a potent μ-opioid receptor agonist that is rapidly metabolised by nonspecific esterases Hence, R's analgesic effects dissipate rapidly upon termination of its infusion. This means that post-operative pain may occur earlier in recovery[1, 2] This study investigated whether morphine (M) or fentanyl (F) given prior to cessation of R-based inhaled anaesthesia with isoflurane (I) or TIVA with propofol (P) would provide immediate post-operative pain control without compromising recovery

Materials and Methods: Following ethics approval and signed consent, 558 patients, >18 years, ASA class I–III undergoing major abdominal surgery were included in 42 centres across 14 countries Patients were randomised to anaesthesia with R + I or R + P. Induction was with R (1 μg/kg), P (0.5 mg/kg) and an infusion of R at 0 5 μg/kg/min. Following tracheal intubation R infusion was reduced by 50%. I was commenced at 0.6% end-tidal and for TIVA group, P was started at 100 μg/kg/min. Anaesthesia was maintained by titrations of R & I or R & P Twenty-five minutes before the end of surgery, either F (0 15 mg) or M (15 mg) was given as a randomised, double-blind dose. A second dose of F (0 05 mg) or M (7 mg) was given post-operatively when moderate or severe pain occurred Subsequent analgesia in recovery room (RR) and upon discharge was provided at the investigator's discretion

Results and Discussion (all times as median, min)

Endpoints	I		P	
	M (N = 142)	F (N = 135)	M (N = 138)	F (N = 136)
Time to. – Spontaneous respiration	6 0	8 0	8 0	8 0
– Extubation	9 0	10 0	11 0	11 0
– Aldrete score >9	11 5	12 5	15 0	14 0
None/mild pain at Aldrete >9 (%)	49	48	48	42
% patients given 2nd opioid dose	91	98	89	93
Time to 2nd opioid dose (min)	21 0	21 0	24 0	26 5
RR Discharge eligibility (min)	87 0	91 5	97 0	103 0

R with I or P provided good anaesthesia. Administration of F or M before termination of R gave good pain control in the immediate post-operative period and did not delay recovery. Proportions of patients reporting severe pain at Aldrete >9 were: 28% (F) and 21% (M) receiving R + I and, 26% (F) and 21% (M) receiving R + P The most common adverse events were post-operative nausea (45–48%), vomiting (9–12%) and shivering (6%); which occurred with equal frequency across both R + I and R + P groups.

Conclusions: For major abdominal surgery, F or M administered ca. 25 mins prior to discontinuing R-based anaesthesia provides effective transitional analgesia in the immediate post-operative period without affecting the rapid recovery seen with R or eligibility for RR discharge. Further studies should be designed eg utilising NSAIDs and opioid combinations to further optimise transitional analgesia

Supported in part by a grant from Glaxo Wellcome

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A.616 Opioid-sparing effect of tenoxicam in the management of postoperative pain. Influence of different dosage regimens

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Background: The use of non-steroidal anti-inflammatory drugs (NSAID's) either alone or in combination with opioids, appear to be increasing in the management of postoperative pain (1, 2) In a double-blind randomized study we investigated the efficacy of tenoxicam, an intravenous (i v.) injectable NSAID, in the management of postoperative pain, when used in two different doses (20 mg and 40 mg), in patients undergoing major orthopaedic surgery

Materials and Methods: In the study were included 72 patients, ASA I–II, well matched for characteristics, scheduled for total hip arthroplasty under spinal anaesthesia. They were randomly allocated in three groups to receive 60 min before surgery either 20 mg i v tenoxicam (group A, n = 24), or 40 mg i.v. tenoxicam (group B, n = 23), or 2 ml of saline (group C, n = 25) In the postoperative period all patients had the possibility of intramuscular pethidine administration (1 mg/kg) on demand. Postoperative pain scores assessed on a visual analog scale (VAS, 0–10) and opioid requirements were recorded at 3, 6, 12, 18, 24 h after motor and sensory restoration.

Results: Our results are summarized in the table. Both tenoxicam groups had lower pethidine consumption (A: 167 ± 47 mg, B: 156 ± 39 mg) when compared to control group (278 ± 47 mg), Bonferroni p-value < 0.0001

VAS	Group A	Group B	Group C	ANOVA P-value
3 h	2.4 ± 0.3	1.9 ± 0.4$^{\blacktriangle}$	3.9 ± 0.5*	<0.0001
6 h	2.9 ± 0.5	2.3 ± 0.4$^{\blacktriangle}$	4.3 ± 0.5*	<0.0001
12 h	3.3 ± 0.5	2.9 ± 0.4^{+}	4.7 ± 0.6*	<0.0001
18 h	3.7 ± 0.5	3.4 ± 0.5	5.0 ± 0.7*	<0.0001
24 h	4.3 ± 0.6	4.0 ± 0.5	5.4 ± 0.7*	<0.0001

Multiple paired comparisons between groups with Bonferroni p-value: *C vs A and B, $p < 0.0001$, $^{\blacktriangle}$B vs A, $p < 0.001$, $^{+}$B vs A, $p = 0.05$.

Conclusion: Both tenoxicam dosage regimens are effective in the management of postoperative pain as they reduce significantly the postoperative mean pethidine consumption. However the dose of 40 mg seems to offer better quality of pain relief than the dose of 20 mg in the immediate postoperative period of 12 h.

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A.617 Oral naloxone in opioid-associated constipation: an intra-individual controlled study

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Background: Opioid-related constipation is one of the most frequent side effects of chronic pain treatment. Enteral administration of naloxone while blocking opioid action at the intestinal receptor level has low systemic bioavailability due to marked hepatic first-pass metabolism. Clinical experience in treating opioid-induced constipation with enteral naloxone is limited to case reports (1). The aim of this study was examine the effects of oral naloxone on opioid-associated constipation in an intraindividually controlled manner.

Material and Methods: After IRB approval chronic cancer pain patients with oral opioid treatment and constipation were enrolled in this study. Constipation was defined as lack of laxation and/or laxative therapy in at least three out of six days. Laxation and laxative use were monitored for the first six days without intervention ("pre-nalox" period). Then, oral naloxone was started and titrated individually between 3 × 3 to 3 × 12 mg/d depending on laxation and withdrawal symptoms. After the four-day titration period, patients were observed for further six days ("nalox" period). The Wilcoxon Signed Rank Test was used to compare number of days with laxation and laxative therapy in the two study periods.

Results and Discussion: Of the 20 patients studied, four patients did not reach the "nalox" period due to death, operation (due to underlying malignancy), systemic opioid withdrawal symptoms, or therapy-resistent vomiting. Of the 16 patients who completed the study, 15 were treated with morphine with a median dose of 239 mg/d during the pre-nalox and 252 mg/d during the nalox period (p = ns). One patient was treated with buprenorphine. The mean naloxone dose in the "naloxone" period was 18.9 mg/d. In the 6 day "nalox" compared to the "pre-nalox" period, the number of days with laxation increased from 2.1 to 3.6 ($p < 0.01$) and the number of days with laxative medication decreased from 6 to 3.4 ($p < 0.01$). Mild withdrawal symptoms such as restlessness, sweating, and nausea were observed in 9 patients with daily doses of 3 × 6 mg naloxone. Moderate side effects were observed in 2 patients following accidental single dose administration of 36 mg naloxone resulting in yawning, sweating, shivering, and increase of pain. Some of the patients reported mild or moderate abdominal propulsions and/or abdominal cramps shortly after naloxone administration. All side effects terminated after 0.5 to 6 hours.

Conclusion: This first controlled study demonstrates that orally administered naloxone improves symptoms of opioid associated constipation and reduces laxative use. To prevent systemic withdrawal signs, therapy should be started with low doses and patients carefully monitored during titration.

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A.618 Comparison of morphine and tramadol in patient-controlled analgesia after microvascular breast reconstruction

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Background: Tramadol is a weak opioid analgesic, which efficacy has not yet been compared with morphine in patient controlled analgesia (1). Therefore, we studied the dose requirements and side effects of morphine and tramadol administered by patient controlled analgesia (PCA).

Materials and Methods: After approval by the Ethics Committee, 54 consenting ASA I–II women undergoing breast reconstruction used PCA (Graseby 3300) for postoperative pain for 42 hours. All patients had isoflurane-nitrous oxide anaesthesia and received fentanyl 3 μgkg^{-1} at the induction followed by fentanyl 1–2 μgkg^{-1}h^{-1}. In the recovery room patients were randomised to receive in a double-blind fashion either i.v. 1 mg morphine or i.v. 10 mg tramadol increments given every 2 min by the anaesthetist (loading) until they were painfree. PCA was then commenced. The bolus dose was morphine 45 μgkg^{-1} or tramadol 450 μgkg^{-1} with the maximum of six times an hour. The drug solution contained either morphine 2 mgml^{-1} or tramadol 20 mgml^{-1} in a blinded fashion. The lockout period of the PCA pump was 5 min. Patients were assessed for pain (VAS) and side effects before and after the loading and at 3, 6, 18, 30 and 42 h.

Results and Discussion: Both groups had similar demographics. In the recovery room mean morphine and tramadol consumption was 10 mg and 137 mg (ratio 1:14) and on the ward altogether 59 mg and 628 mg (ratio 1:11). 11 patients in the tramadol group and one patient in the morphine group had nausea during loading ($p < 0.001$, Mann-Whitney U). There was no difference in the quality of analgesia (VAS) or incidence of side effects, such as nausea, vomiting, pruritus and sedation between the groups after loading in the recovery room and on the ward.

Conclusions: Morphine: tramadol efficacy ratio varied from 1:11 to 1:14 in this study. In these both groups the pain relief was similar. Tramadol caused more nausea during loading.

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A.619 Tramadol infusion *vs* morphine PCA for post-Caesarean section pain: a pilot study

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Introduction: Tramadol, a non-addictive opioid, induces scant respiratory depression and less sedation than pethidine and morphine; given with PCA following laparotomy, tramadol 640 mg 24 hr^{-1} provides equivalent analgesia to pethidine 604 mg 24 hr^{-1} [1, 2]. This data suggests its suitability for addition to postoperative IV fluids to provide analgesia. We compared the efficacy and side effects of tramadol infusion (tramadol) with morphine PCA (morphine) until 48 hours after Pfannenstiel laparotomy.

Method: With Ethical Committee approval and patient consent 40 patients randomly received tramadol 1.5 mg kg^{-1} or morphine 0.15 mg.kg^{-1} as analgesic adjunct to anaesthesia, followed by infusion of tramadol (150 mgs in 500 mls dextrose saline; 30 ml.kg^{-1}. 24 hrs^{-1}) or morphine PCA (1.5 mg demand, 6 min lockout), respectively. Postoperatively, patients were assessed hourly by nurses, daily by Pain Service doctors and, independently, by AvdB, for pain, sedation, satisfaction, nausea, vomiting, headache, dizziness, drowsiness, pruritis, mobility, sweating, heart rate, blood pressure, respiratory rate, rescue analgesia/antiemesis, urinary retention, backache, and nurses comment using standard objective and subjective protocols. Analysis used Fishers Exact, Chi-squared, Mann Whitney U and Students 't' tests. ($p < 0.05$ significance).

Results: Groups (N = 20 each) were comparable. Mean opioid consumption per each 24 hr. period were tramadol 834 mgs and 741 mgs (total 1576 mgs in 48 hrs); morphine 64 mgs, 41 mgs (total 105 mgs in 48 hrs). Observers and patients rated pain relief, patient satisfaction, and all parameters similarly, except that morphine induced more dizziness ($p < 0.006$), drowsiness ($p < 0.0040$) and pruritis ($p < 0.0150$).

Discussion: Use of conventional opioids for postoperative analgesia is open to abuse by staff and patients. PCA is costly (pump and disposables), and prone to discontinuation through technical problems.

Conclusion: Addition of tramadol to routine postoperative IV fluids is a simple, efficacious and cost effective alternative to morphine PCA, with advantages of inducing less dizziness, drowsiness and pruritis.

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A.620 Patient-controlled analgesia with pethidine after elective gastrectomy: epidural *vs* intravenous routes

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Background: Patient-controlled epidural pethidine has been reported to produce high quality postoperative analgesia after caesarean section. (1) This randomised controlled study aimed to compare the effectiveness of patient-controlled epidural with intravenous pethidine after major abdominal surgery.

Method: After local ethical committee approval and informed consent, ASA I–III patients scheduled for elective gastrectomy were recruited. A standardised general anaesthetic technique supplemented by thoracic epidural anaesthesia was employed. After reversal of anaesthesia, the patients were randomised in a double-blind manner to either receive PCA pethidine through the epidural or intravenous route A bolus dose of pethidine 25 mg was first administered when the visual analogue score (VAS) for pain >40 mm (time zero) Ten minutes later, PCA was started with a 10 mg bolus and 10 min lockout VAS for pain, a 4-point sedation score and cumulative pethidine consumption was recorded at 1 h, 4 h, 8 h, 24 h and 48 h The presence and severity of nausea, vomiting and pruritus were recorded for the periods 0–8 h, 8–24 h and 24–48 h. The overall patient satisfaction was recorded using the VAS. Blood samples for assay of serum pethidine and norpethidine were taken at 0 h, 4 h, 8 h, 24 h and 48 h Statistical analysis was performed with Chi-square, Student-t or Mann-Whitney U test, $p < 0.05$ being significant.

Results & Discussion: 30 patients have completed the study There was no difference in age, sex, ASA status, VAS for pain at rest and coughing, sedation score, incidence of side effects and length of hospital stay between the two groups. Pethidine consumption and serum pethidine levels were lower in the epidural group up to 24 h ($p < 0.05$) There was no difference in norpethidine levels Overall patient satisfaction was similar.

Conclusion: Although epidural PCA pethidine achieved lower pethidine consumption and serum pethidine levels, it did not appear to be clinically important when compared to the intravenous route.

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A.621 Addition of adrenaline to pethidine for patient-controlled epidural analgesia

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Background and Goal of Study: Addition of adrenaline was found previously to increase the duration of analgesia and reduce systemic absorption from a single dose of epidural pethidine after Caesarean section.[1] This study aimed to investigate the addition of adrenaline to pethidine for patient-controlled epidural analgesia (PCEA).

Materials and Methods: Ethics Committee approval and informed consent were obtained In a randomized, double-blind study, we assigned 80 patients having elective Caesarean section to receive postoperative analgesia in the first 24 h by patient-controlled epidural analgesia (PCEA) using pethidine 5 $mg.ml^{-1}$ with (Group Pa) or without (Group Po) adrenaline 5 $\mu g.ml^{-1}$. The PCEA settings (bolus 25 mg, lockout interval 10 min, 4-h maximum dose 150 mg) were identical. Pain at rest and on coughing, nausea, pruritus and sedation were measured by visual analogue scale at 2 h, 6 h and 24 h. Drug consumption and patient satisfaction were recorded Data were analysed using Student's t-test, the Mann-Whitney U test and Fisher's exact test $P < 0.05$ was considered significant.

Results and Discussion: Seventy-eight patients completed the study Patient characteristics, pain scores (Fig 1) and satisfaction were similar between groups. There was a trend towards lower mean 24 h consumption of pethidine in Group Pa (231.5; SD 140.5 mg) vs Group Po (289 5; SD 139.5 mg, $P = 0.07$). Patients in group Pa had greater nausea at 2 h and 24 h and greater pruritus at 2 h.

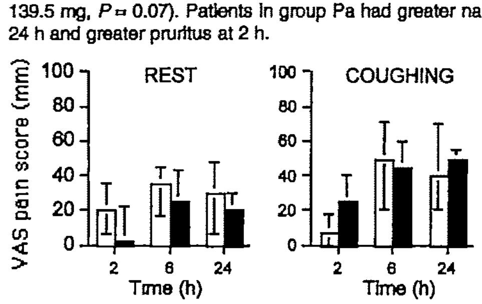

Fig 1 VAS pain scores (median, interquartile range) □ = Group Pa ($n = 40$), ■ = Group Pa ($n = 38$)

Conclusion: Addition of adrenaline to pethidine for PCEA does not have significant clinical advantages

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A.622 Safety of sufentanil postoperative patient-controlled analgesia after renal transplantation

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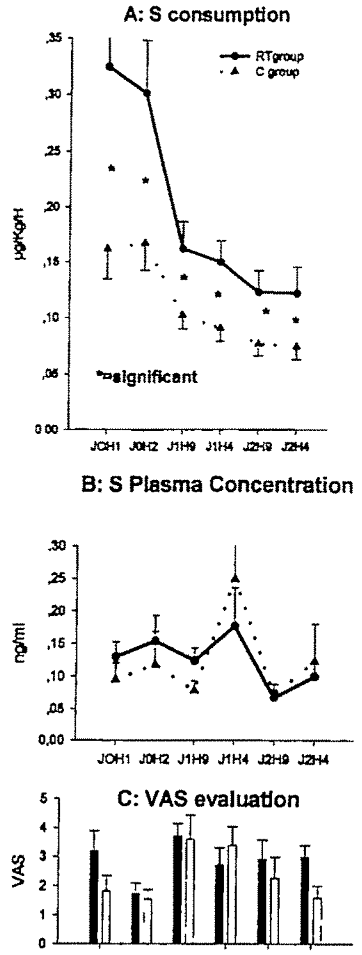
Postoperative pain relief in kidney transplanted patients remains a problem i.e. morphine is not safe as active metabolites accumulate (1). The safety of S analgesic during RT (2) and in patients with chronic renal failure (3) has been studied, so was S PCA for postoperative analgesia in normal patients (4) We assessed the efficiency and safety of S PCA for postoperative pain relief after RT

Methods: After informed consent and institutional approval, 22 patients (aged 21 to 65 years) were studied: 11 undergoing RT were compared with 11 control patients (C) undergoing abdominal surgery After general anesthesia with S atracurium and isoflurane, a PCA pump (Abbott Life Care) was connected for intravenous S analgesia during 48 hours, as follows background infusion 2.5 μg/h, bolus 5 μg, lock out time 5 min and maximum dose 80 μg/4 h Plasma S concentrations (ng/ml) are assessed by radioimmunoassay (4), PCA consumption (μa/kg/hour), quality of analgesia (Visual Analogue Scale-VAS 0 to 10) and side effects were recorded at 1 (J0H1) and 2 (J0H2) hours after extubation and twice daily at 9 am and 4 pm during the first (J1H9, J1H4) and the second (J2H9, J2H4) postoperative days Comparison was assessed by Student t Test, $p < 0.05$ was significant. Results are presented as mean ± SEM


A: S consumption

B: S Plasma Concentration

C: VAS evaluation

Results: S consumption was significantly more important in RT group than in C group (fig. A), however plasma S (fig B) concentrations were similar as well as the VAS (fig. C). Side effects such as sedation and nausea-vomiting were rare and their incidence equal in the two groups

Conclusion: This study shows that S PCA can safely be used after

RT Although S consumption was higher in the RT group, plasmatic concentrations were similar. Satisfactory VAS were obtained in both groups.

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A.623 Why patients feel positive about patient-controlled analgesia

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Background and Goal of Study: Previous studies have shown that patients report greater satisfaction with patient controlled analgesia (PCA), than with conventional intramuscular analgesia [1]. Satisfaction with PCA was not accompanied by an increase in the amount of analgesia used or low pain scores [1]. Superficial questions about satisfaction are problematic, as they tend to produce positive results [2] The goal of this study was to examine why patients respond positively to PCA and discover what variables influence satisfaction.

Materials and Methods: 200 patients completed a questionnaire about their experiences of PCA, 24 to 72 hours after PCA had been withdrawn. The questionnaire covered the following topics: strategies for using PCA, pain relief, side-effects, safety, advantages and disadvantages of PCA, worries associated with its use and control over pain. The Chi-squared test was used to compare responses between groups. $P < 0.05$ was considered significant.

Results and Discussion: Patients who were 'extremely positive' about PCA ($n = 83$), were compared with those who were not ($n = 117$). Patients who were 'extremely positive' reported significantly better pain relief, had better control over their pain, found that their machine worked well, they could use their machine whenever they liked, felt safer using PCA and were less likely to feel peculiar in the head. These patients were less worried about overdosing themselves or the machine giving them too much drug There were no differences in the strategies that they employed to control their pain or other side-effects. Although the 'extremely positive' patients achieved control over their pain, more of the significant answers centred around safety

Conclusion: Patient satisfaction is a complex issue in which issues of safety play the dominant role.

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A.624 Postoperative pain after low-dose intrathecal morphine in elective laparoscopic cholecystectomy

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Background: Postoperative pain after laparoscopic cholecystectomy can be important especially in the early postoperative hours[1]. The aim of this study was to assess the effects of a low-dose of intrathecal morphine injected prior to elective laparoscopic cholecystectomy on pain scores, postoperative analgesic requirements and side-effects.

Methods: After ethical approval and informed consent had been obtained, 32 adults ASA I–II (aged 20–70), were randomised into two groups: spinal, "S" and control, "C". The S group had an intrathecal injection of 100 or 75 μg of morphine (75 for those aged $\geq$ 65 years), before general anaesthesia The C group had a subcutaneous injection of a saline solution in the L3–L4 interspace. For all patients, iv morphine PCA was used as rescue analgesia. Postoperative morphine requirements after 20 h, pain scores at rest and while coughing, sedation, time to first food intake, nausea and vomiting, urinary retention, quality of sleep, time to discharge, and satisfaction were assessed by an observer blinded to the study. For statistical analysis we used Student's *t* test, Mann Whitney rank sum test, chi-square test and ANOVA for repeated measures as appropriate.

	Postoperative hours				*P* *S vs C
	2	4	6	20	
Spinal (n = 15)					
Morphine (mg) mean ± SEM	3 2 ± 2	5 3 ± 2	6 5 ± 3	10 ± 5	
Pain (VAS, mm) rest mean ± SD	18 ± 12	18 ± 17	11 ± 12	8 ± 12	
Cough mean ± SD	35 ± 17	30 ± 15	24 ± 19	20 ± 12	
Control (n = 17)					
Morphine (mg) mean ± SEM	6 7 ± 3	10 ± 2	13 ± 3	20 ± 6	p = 0.04*
Pain (VAS, mm) rest. mean ± SD	37 ± 20	29 ± 21	26 ± 19	20 ± 12	p = 0 001*
Cough mean ± SD	56 ± 20	57 ± 20	48 ± 24	40 ± 20	p = 0 001*

Results: No significant difference was noticed with regard to patients characteristics, anaesthetic requirements, nausea and vomiting, sedation, quality of sleep and time to discharge. Morphine requirements and pain scores were significantly lower in the S group (table). The incidence of urinary complications requiring treatment was significantly higher in the S group (27% vs 6%, $p = 0.01$).

Conclusions: Under the conditions of our study, low dose intrathecal morphine provides effective analgesia in laparoscopic cholecystectomy, at the expense of an increased incidence of urinary complications.

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A.625 Effect of intrathecal low-dose morphine for postoperative analgesia after total hip replacement

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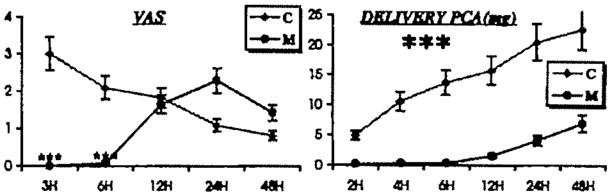
Background and Goal of Study: A significant increase in the use of intrathecal opioids for postoperative analgesia has been observed in the last few years[1, 2, 3]. Our purpose in this study was to evaluate the quality and duration of postoperative analgesia using low dose intrathecal morphine and estimate its safety and concomitant adverse effects.

Methods: After ethical approval and informed patient consent was obtained, 25 patients (ASA 1–2) aged 62 to 80 years and weighting 44 to 115 Kg, undergoing total hip replacement under spinal anaesthesia using hyperbaric bupivacaine 0.5% were randomized to receive either saline (C group) or 0.1 mg morphine (M group) in a double-blind manner. Postoperative analgesia was provided using intravenous morphine by a Patient Controlled Analgesia device. Pain was assessed using VAS and morphine consumption during the first 48 h postoperatively Results were analysed by χ^2 test and student t-tests, $p < 0.05$ was considered significant.

Results: VAS was significantly reduced in the M group during the first 12 hours compared with the C group (fig.1). Morphine consumption was significantly higher in the C group compared with the M group throughout the postoperative period (fig.2). There were no difference in the incidence of postoperative nausea and vomiting and pruritus between both groups. Urinary retention was significantly higher in the M group.



Conclusion: The use of intrathecal morphine (0.1 mg) provides better postoperative analgesia than Bupivacaine alone and reduces analgesic requirements with no increase in adverse effects except urinary retention.

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A.626 Comparison of intrathecal morphine sulphate and morphine hydrochloride as analgesics for hip arthroplasty

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Background & Goal of Study: Intrathecal (I.t.) morphine produces analgesia in the postoperative setting (1) The aim of our study was to compare I t. morphine sulfate (MS) and i.t. morphine hydrochloride (MHCl) for postoperative analgesia with respect to duration of analgesia as well as side effects.

Materials & Methods: The retrospective analysis included 103 consecutive patients after total hip arthroplasty. In all patients spinal anaesthesia (L1–5) was performed with plain 0.5% bupivacaine 3.5–4 ml together with 0.1 mg MS in 52 patients and 0.1 mg MHCl in the following 51 patients. Duration of analgesia was defined as time between I.t. drug administration and first postoperative analgesic treatment. Nausea, emesis, pruritus, sedation, and respiratory depression were evaluated. Data are given as median values and ranges, Mann-Whitney-Wilcoxon and the Fisher's exact test were used Significance was assumed at the 5% level of probability

Results and Discussion: There were no significant differences in physical characteristics between MS and MHCl treated patients. In patients who received MS the median value for first postoperative analgesic treatment was 540 min (180–1440) vs. 390 min (180–1440) in patients treated with MHCl Significantly more patients were completely pain-free within the first 6 hours after i t MS ($p < 0.05$) After 24 hours 13 out of 52 MS treated patients were still pain-free vs 4 out of 51 patients ($p < 0\ 05$) The frequency and type of side effects were similar for both groups There was a tendency for fewer demands for postoperative analgesic treatment in patients who received i t MS.

Conclusion: MS, given intrathecally, provided excellent analgesia after total hip arthroplasty. An explanation for the longer duration of analgesia of i t MS might be the higher pH-value compared to MHCl

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A.627 Efficacy of intrathecal neostigmine for the relief of postinguinal herniorrhaphy pain

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Background and Goal of Study: Recently intrathecal administration of neostigmine at varid doses has been reported to produce analgesia without neurotoxicity in animal studies and human volunteers with experimental pain The present study was undertaken to evaluate the efficacy and safety of intrathecal neostigmine in the relief of pain in patients after inguinal herniorrhaphy surgery.

Materials and Methods: After giving their consents 60 men scheduled for elective inguinal herniorrhaphy with spinal anesthesia were randomly enrolled into 3 groups· Group I ($n = 20$) received intrathecal (IT) tetracaine 15 mg, group II ($n = 20$) received IT tetracaine 15 mg + neostigmine 50 μg, and Group III ($n = 20$) received tetracaine 15 mg + neostigmine 100 μg Onset of anesthesia, duration of analgesia, vital signs, and incidence of adverse effects were recorded for 24 hours post drug. Data were expressed in mean ± SEM A value of $p \leq 0.05$ was regarded as statistically significant difference.

Results and Discussion: The demographic data were similar for the three groups. Onset of anesthesia (time to T6 sensory block) was significantly faster in Group III (1 6 ± 0 7 min) and Group II (2 3 ± 0.9 min.) compared to Group I (5 5 ± 1.9 min) Motor block (time to lift leg) was greatly prolonged in Group III with a average of 6 4 hr compared to 4 hr. in Group I Group III also showed a later onset of post surgical pain ($\bar{x} = 523$ min) than Group I ($\bar{x} = 243$ min.) There was a significantly higher incidence of adverse effects associated with IT neostigmine, especially nausea and vomiting, 15% in Group I, 40% in Group II, and 50% in Group III

Conclusion: Our study showed that intrathecal neostigmine at 50 μg or 100 μg enhanced the onset of tetracaine anesthesia and provided analgesia lasting about 6–9 hours. However, there are increased incidences of prolong motor blockade and nausea or vomiting

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A.628 A new N-type calcium channel blocker SNX-111 administered intrathecally for acute postoperative pain

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Introduction: Voltage-dependent calcium channel conductance is essential for the nervous system to signal a painful event Intrathecal administration of calcium channel blockers of the L-type to induce antinociception proved to be ineffective (1). The present investigation was designed to evaluate two different dosages of the new N (neuronal)-type calcium channel blocker SNX-111 administered intrathecally in patients with acute postoperative pain

Methods: After IRB approval, 15 patients participated in this multicenter, randomized, phase II, double-blind pilot study to assess the safety and effectiveness of SNX-111 after total hip replacement The patients were provided with an intrathecal catheter for postoperative pain management They received 2–3 ml of bupivacaine 0.5% with epinephrine (5 μg/ml) for intraoperative anesthesia. Immediately prior to surgery, a continuous infusion of either placebo ($n = 6$), 0 7 μg/hr ($n = 6$) or 7 μg/hr ($n = 3$) of SNX-111 was started and continued throughout the operative procedure as well as for 48 h into the postoperative period Routine pain assessments were performed every 4 h by means of a *visual analog scale* (VAS) ranging from 0 = no pain to 100 = worst imaginable pain Assessments were started 4 h after surgery and continued for 48 h postoperatively Systemic morphine consumption administered by patient-controlled analgesia (PCA) was recorded during the study period. Data are expressed as mean ± SD. Statistical comparisons were made between the placebo and the low dose groups using ANOVA and unpaired t-test, $p < 0\ 05$ was considered statistically significant.

Results: The three patient groups were comparable with respect to age, weight, and height. No statistical difference was found between the placebo group and those patients receiving SNX 0 7 μg/hr with regard to pain scores and morphine consumption All three patients receiving 7 0 μg/h and one patient with 0.7 μg/h of the study drug had to be discontinued after 24 h due to adverse events such as dizziness, blurred vision, and sedation. VAS scores and morphine consumption within the first 48 hours after surgery are displayed in the Table

Discussion: The existence of three distinct types of calcium channels (L, T, and N-type) in sensory neurons are reported in the literature (2) While the administration of L-type calcium channel blockers such as verapamil, diltiazem, and nicardipine without additional morphine proved ineffective (1), intrathecal administration of SNX-111 (N-type) appears to have an antinociceptive effect useful for perioperative pain relief. The higher dose of 7.0 μg/h, however, was associated with too many adverse events in this investigation to be recommended for routine clinical use The optimal dose of SNX-111 useful for clinical practice may lie between the two doses studied.

	VAS8	VAS16	VAS24	VAS48	MOR24	MOR48
Placebo	38 ± 38	20 ± 22	32 ± 31	10 ± 11	22 ± 15	35 ± 22
0.7 μg/h	20 ± 16	18 ± 15	19 ± 17	21 ± 18	15 ± 12	29 ± 23
7 0 μg/h	14 ± 24	12 ± 16	9 ± 11	–	24 ± 10	–

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A.629 The efficacy of pre-incisional and post-incisional bupivacaine infiltration on postoperative pain in inguinal herniorrhaphies

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Background & Goal of Study: Control of postoperative pain is an important factor in preventing the modification of the excitability of the dorsal horn neurons (1) The aim of our study is to compare preincisional and postincisional infiltration of the surgical area with bupivacaine.

Materials & Methods: With the approval of the ethic committee and informed consent, 24 male patients ages between 25–70 for elective lateral inguinal hernia repair were included in the study. All patients received balanced inhalational anaesthesia The patients were randomized into two groups Preincisional group (Group I, $n = 12$) and postincisional group (Group II, $n = 12$) Group I consisted of patients receiving 40 ml 0 25% bupivacaine wound infiltration at 5 min before skin incision and the same procedure was performed for group II before skin closure. Postoperative pain medication included meperidin (IM) or metamizol (PO) as needed 48 hours after surgery the pain was recorded with visual analogue scala (VAS) and verbal rating scala (VRS). First analgesic requirement time and total analgesic consumption were recorded Comparison between groups was based on the Mann-Whitney-U test and nonparametric methods of variance analysis

Results & Discussion: Postoperative pain scores were lower in the preincisional group than in the postincisional group although the difference had not been significant ($p > 0\ 05$). First analgesic requirement time was significantly shorter in group I compared to group II ($P < 0.05$) The amount of total analgesic used was highest in postincisional group ($p < 0\ 05$) The findings of Ejlersen at al (2) and the findings in our study suggest that the inhibition of peripheral sensitization may be of major importance in avoiding the development of acute pain and may explain why prevention is important in handling operative pain

Conclusion: We conclude that preincisional infiltration of the surgical wound with bupivacaine is a more effective method of providing postoperative analgesia compared to postincisional infiltration

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A.630 Analgesic effect of low-dose ketamine administered during knee surgery

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Background and Goal of the Study: Ketamine (K) is in low doses an uncompetitive NMDA antagonist. The purpose of this study was to evaluate the analgesic effects of K in patients undergoing knee crucrate anterior ligamentoplasty under arthroscopy.

Materials and Methods: 45 ASA 1–2 patients were enrolled in a prospective, double-blind and randomized study. They were allocated in 3 groups: group 1 (G1) received 0.15 mg/kg of K after induction and before surgical incision and placebo at the end of surgery; group 2 (G2) received placebo after induction and before surgical incision and 0 15 mg/kg of K at the end of surgery; group P (GP) received placebo at the beginning and the end of surgery. All the patient were anesthetized with propofol for induction and maintenance. Sufentanil (bolus of 0 2 μg/kg then 0.2 μg/kg/h) was started 10 min after incision Postoperative analgesia was provided by IV patient controlled analgesia morphine (bolus: 1 mg, lockout period: 5 min). Pain was assessed using 10 cm visual analogic scale (VAS) and morphine consumption was noted during 24 h postoperatively every 4 hours and during first physiotherapy period at day 1. Delay of first demand and side effects were recorded. Results were analysed by ANOVA and unpaired-t-test $p < 0.05$ was considered significant.

Results: Morphine consumption was continuously less for the 24 h of the study period and during physiotherapy for patients who received K either before or after surgery compared to placebo (table) However, no difference appeared between groups 1 and 2. VAS pain scores at rest were similar between groups. During the first physiotherapy period pain score were similar between groups but morphine consumption was higher in GP with a lesser flexion (table)

Table

	Delay of first demand (min)	Total morphine dose (mg)	First physiotherapy period	
		first flexion (°)	M (mg)	
G1	27 2 ± 23*	28 2 ± 18 4*	47 ± 13*	1 2 ± 0.4*
G2	29 8 ± 22*	24 2 ± 17 8*	46 5 ± 12*	1.4 ± 0 7*
GP	9.5 ± 7 2	49 7 ± 24 1	35 ± 10	3 8 ± 1.7

* $p \leq 0\ 05$ with GP, mean ± sd

Side effects were comparable in three groups. No psychic disorder appeared in K groups

Conclusion: No preemptive effect was obtained with K in the present study. However, in two groups, peroperative administration of a low dose K had the benefit to decrease postoperative morphine consumption and to improve analgesia during physiotherapy.

A.631 Pre-emptive analgesia induced by epidurally administrated liposome encapsulated bupivacaine

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Introduction: Postoperative complications can be reduced with extended monitoring and pain relief. Liposomes encapsulated anaesthetics get us nearer to this concept as the encapsulation of bupivacaine into liposomes resulted in a bupivacaine release of 48 h. We compared the morphine-sparing effect of preoperative epidural liposome associated bupivacaine administration (group Lipo) versus preoperative epidural bupivacaine administration (group Bupi) in a double blind placebo controlled clinical setting.

Methods: After local Ethics Committee Approval and informed consent 30 patients, undergoing major abdominal surgery were divided in three groups: each group received before surgical incision and after a 3 ml epidural test-dose of lidocaine 2% with 1/200.000 adrenaline (L2-level), an epidural injection of either 10 ml liposome associated bupivacaine, plain bupivacaine or saline (group Placebo). A TIVA with propofol, sufentanil and vecuronium standardized to all groups ensued. After surgery, decuranization and regaining consciousness pain sensation was monitored with the Visual Analog Scale (VAS) and the level of dermatomal block was assessed by loss temperature and pinprick. All patients received a PCA-pump with morphine (2 mg bolus, lock out time 5 min, maximal dosis 16 mg/4 h) to alleviate their pain. Differences between groups were identified using ANOVA. The Newman-Keuls test was used to detect intra-group differences.

Results: The three groups were homogenous regarding population characteristics and surgery time. The spread of sensory dermatomal block was an overall 2 to 3 dermatomes smaller in group Bupi. The VAS were lower and the morphine consumption less (−35% vs placebo, P = 0.13) in the patients of group Lipo vs group Placebo. On the contrary, no differences were observed between the VAS scores of group Bupi and Placebo though the morphine consumption was reduced by 15% in group Bupi (P = NS.)

Summary: Pre-surgical epidural administration of liposome encapsulated bupivacaine reduces post operative pain and morphine requirements when compared to epidural bupivacaine, suggesting a prolonged activity of the liposomal solution

A.632 Pre-emptive analgesia with ropivacaine during breast reconstruction

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Introduction: Preemptive analgesia is an antinociceptive treatment that prevents the establishment of altered central excitability due to high intensity noxius stimuli (1). Experimental data suggests that preadministration of local anesthetics decrease hyperplasticity of the central nervous system and postoperative pain (2) Clinical investigations do not always support experimental data (3). The aim of this study is to evaluate the efficacy of preemptive analgesia, with a correct regional anesthetic technique.

Methods: Twenty women, ASA I–II, scheduled for breast reconstruction were randomly divided in two groups: 10 patients received preemptive analgesia with ropivacaine infiltration 1.5 mg/mL, (100 mL) before the skin incision (group A) and 10 pts in which infiltration was performed with normal saline (group B). In all patients, anesthesia was induced with propofol O_2:N_2O (30:70), vecuronium bromide, isoflurane and maintained with isoflurane. Postoperative pain was evaluated by a blinded observer using VAS in the recovery room and during the following 24 hours postop. Analgesic requirement during this period, if necessary, was recorded. Statistical analysis was performed by ANOVA and T-test. Significance was measured at a level of $p < 0.05$.

Results and Discussion: In group A (VAS 0–1) no pt required any postop analgesia. In group B, all pts (VAS 3–4) required ketorolac for pain control ($p < 0.001$). As reported by Kissin (3), the results of this study suggest that clinical impressive effects of preemptive analgesia are observed when the blockade of noxious stimuli is complete and extended into the initial postop period.

Conclusion: Our results suggest that preop extended infiltration with ropivacaine correctly performed in time, volume and concentration leads to a successfully postop pain control.

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A.633 Olfen (diclofenac sodium) for postoperative analgesia after gynaecological surgery

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Background and Goal of Study: NSAIDs have been found to be effective in post-operative analgesia [1, 2]. This study was performed to evaluate the analgesic efficacy of Olfen (O), and its effect on postoperative requirement for Fentanyl (F), as well its safety

Material and Methods: 30 women, ASA I–II, aged 25–59 yrs, scheduled to abdominal hysterectomy were randomly allocated to standardized premedication and neuroleptanaesthesia. One group of patients (*O*, n = 15) received O in dose 75 mg i/m perioperatively, another, control (*C*, n = 15) – normal saline. Rectocaps of O (100 mg) or 75 mg i/m were given on-demand to patients of *O* group in the first and second postoperative days. VAS (0–10 cm), F requirement, postoperative nausea and vomiting (PONV) or other side effects were registered at awakening and 4, 8, 12 h. Overall the F consumption was evaluated after 24 h. Measurements of bleeding time (BD), platelet count (PC) were investigated before surgery and on 3-d and 7-th day.

Results: Both groups were comparable as to demographic data and duration of surgery (75–80 min.) They needed the same amount of F (0 4 mg). After awakening 20% of *O* group were completely without pain, 40% expected mild pain (VAS 2–3 cm), 33.3% – moderate pain (VAS 4–5 cm), 6.67% – severe pain. At the same time no patient of *C* group had no pain. Mean pain intensity on the awakening in *C* group was between 4–7 cm in VAS; 20% of patients had very severe pain (VAS > 7 cm). During first 4 h after surgery 46.6% of *O* group had no need for analgesia, but 54.4% were given 0.1 mg of F. During 12 h after surgery 33.3% of *O* group had good analgetic effect from 0.75 mg i/m and had no need for opioid, 53.3% were given F 0.1 mg and 13.4% – F 0.2 mg When compared with saline, *O* resulted in a reduction of the cumulative F dose by 1.8 times at 4 h, by 2.5 times at 12 h and by 2.7 times at 24 h 40% in saline group required antiemetic compared with 6.67% in *O* group. There were no significant changes and differences between the groups in BT and PC No bleeding complications occurred in *O* group

Conclusions: 1. O reduces pain and need for opioids after abdominal hysterectomy during the first 4–12 h postoperatively. 2 The use of O in the first postoperative days produces effective analgesia 3. O has been found to be safe for acute postoperative pain relief after abdominal hysterectomy.

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A.634 Validation of predictors of postoperative pain

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Background and Goal of the Study: In a previous study(1), behavioral and psychological factors predictive of the intensity of postoperative pain were investigated on a reference group of 300 patients. It concluded that bad quality of sleep and fear of postoperative pain increased the odds of severe pain by more than 2.5 folds The present study was performed to validate these results on 2 other groups of patients

Patients and Methods: Validation group 1 included 100 patients undergoing orthopedic or intraperitoneal procedures with various anesthetic and analgesic techniques. Validation group 2 included 60 patients (30 undergoing total knee prothesis and 30 undergoing colectomy) with the same anesthetic and analgesic techniques All patients were 18 to 74 years old and answered the same preoperative and postoperative questionnaires used for the reference group. The model of logistic regression developed in the reference group was applied on the 2 validation groups.

Results: (table). While bad quality of sleep remained highly significative in the 2 validation groups, fear of postoperative pain was not validated and gender male increased the risk of postoperative pain only in the validation group 1.

Discussion and Conclusion: Bad quality of sleep reported by the patient emerged as a strong predictor of severe postoperative pain The anesthesiologist should take into account this factor, easy to assess in clinical practice and consider it in the management of postoperative analgesia. Fear of postoperative pain and gender appeared as risk factors, but require further investigations including all potential confusion factors

Odds ratio of high pain compared to low pain in the reference group and the 2 validation groups

Variables	Reference group		Validation group 1		Validation group 2	
	OR adj *	95% CI	OR adj *	95% CI	OR adj *	95% CI
	n = 300		n = 100		n = 60	
Gender						
Women	1.0		1.0		1.0	
Men	1.0	0.6–1.8	3.8	1.1–13.3	1.4	0.2–4.9
Quality of sleep.						
Good (VAS < 5)	1.0		1.0	1.0		
Bad	2.3	1.3–4.0	4.1	1.1–4.9	4.2	1.2–15.3
Fear of postoperative pain.						
No (VAS < 5)	1.0		1.0		1.0	
Yes	2.2	1.2–3.9	2.4	0.7–8.5	1.5	0.4–5.7

OR adjusted*: odds ratio simultaneously adjusted for all variables included in the logistic regression 95% CI: confidence interval for 95% VAS: visual analog scale

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A.635 Postoperative pain assessment: methodology for VAS curve analysis

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Background and Goal of Study: The routine assessment of postoperative pain represents a basic tool for implementing a quality assurance project. The purpose of this study is to describe a methodological approach of visual analogue scale (VAS) curve analysis corresponding to a internal audit The aim is to define analytical tools pointing out problems with postoperative analgesia in selected surgical departments

Materials and Methods: One thousand five hundred patients, undergoing various surgical procedures, were enrolled Patients were evaluated for pain intensity at rest, using VAS during 72 hours in the postoperative period VAS curves registered were pooled in regard to selected surgical specialties. Comparison of VAS curves were conducted using four end-points: VAS max peak amplitude of VAS (cm), T max: time to peak of VAS (h); AUC: area under the time-VAS curve during intervals of 24 hours (cm × h), slope of VAS curve regression line (%). Statistical analysis Data Mean ± SD ANOVA and Student's *t* tests $P < 0.05$ significant

Results and Discussion: Results are presented in Table

	Ortho	Abdo	Plast	O R L	Gyn	Opht	Neuro	Uro
n	466	340	112	110	99	84	76	40
VAS max	3.1	2.5	2.6	2.1	3.0	0.8	3.7	1.9
	±2.3	±2.6	±2.7	±2.1	±3.0	±2.0	±2.8	±2.7
T max	12	1	1	6	1	0	12	4
AUC→24 h	56.6	51.2	47	36.4	57.6	14.2	73.2	32.5
AUC→48 h	46	35.4	34.5	21.7	43.9	6.2	60.9	26.9
AUC→72 h	35.4	19.6	21.9	7.1	30.2	0	48.6	21.4
Slope	−1.84%	−2.75%	−2.18%	−2.54%	−2.38%	−1.38%	−2.14%	−0.96%

Our study describes four end-points: VAS max and AUC determine severity of acute pain, T max points out the timing of the VAS peak, and the slope of regression line could be considered as the reflect of the natural history of postoperative pain. These items rapidly permit pointing out problems with postoperative pain management at the scale of the hospital.

Conclusion: Designing tools to guide physicians and nurses to initiate and modify analgesic treatments expertly, is an immediate challenge for implementing a quality assurance project.

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A.636 Implementation of a postoperative pain protocol: a stepwise approach

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Introduction: A good postoperative pain management can reduce postoperative morbidity. Our institution consists of a 840 beds regional hospital with a reference function. The Departement of Anesthesiology consists out of 30 staff members and assistants We tried to implement a postoperative pain protocol for: improvement of postoperative pain scores, standardization of prescriptions, fine adjustments of individual pain treatment by the Nursing Department and prevention of postoperative pain by a regular score system.

Aim of the Study: In our protocol for postoperative pain management we used a multimodal medication scheme, which is based on the WHO analgesic stepwise approach. The base of the protocol is peripheral acting analgesic (proparacetamol and/or NSAID) administrated on regular basis Using an algorithm that includes the pain score, degree of sedation, the respiratory function and the circulatory state, the ward nurse can decide on an independent, but safe medicolegal method to administrate an opioid if pain rating scores are too high By scoring the patients on a regular basis we can prevent severe postoperative pain.

Method: The evaluation of our protocol consists of two phases:

- Phase I: using a descriptive questionnaire the postoperative patient is evaluated. This phase is before implementation of our protocol from June 1996 until October 1996 100 postoperative patients were evaluated
- Phase II where we will evaluate after implementation of the postoperative pain protocol

Results: In general we believed that postoperative pain management without algorithms was satisfactory. But in this phase I-evaluation we found that 14 patients out of 100 scored the postoperative pain treatment as clearly insufficient. All kind of surgery was included. Preoperative information about postoperative pain was only sufficient in 22% of all patients. 30% of the patients were evaluated by the ward nurses on a numerical pain rating score. Only 50% of the patients are dismissed from the PACU with a pain score less than 5/10 In the first 24 hours 40% of the patients experienced moderate to severe pain (VAS > 4).

Conclusion: We believe that a good postoperative pain management has to be based on a multimodal postoperative pain algorithm, where nurse controlled analgesia can ameliorate postoperative pain scores

A.637 Acute pain management: description of a performance quality indicator

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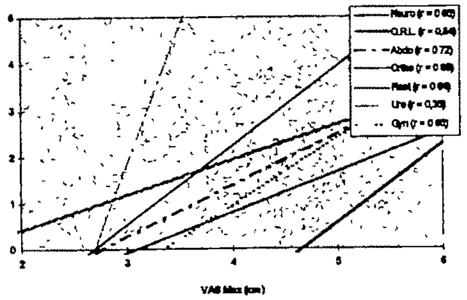
Background and Goal of Study: The traditional method of providing postoperative analgesia is the use of opioids But, unrelieved acute pain is still reported to be a rather common clinical problem which may be related to inadequate routines for treatment (1) The aim of this study was to describe a performance indicator of pain management quality, permitting comparison between different surgical specialities at the scale of a general teaching hospital.

Materials and Methods: 1,500 postsurgical patients above 15 years old were enrolled Visual Analogue Scale (VAS) scores at rest and *pro re nata* opiate administration, expressed in mg morphine equivalents, were recorded every 4 hours during 72 hours in the postoperative period. The relationship between VAS scores and morphine amounts given was studied in different surgical specialities Statistical calculations included descriptive statistics, and weighted Pearson correlation coefficients.

Results and Discussion: Correlation coefficients (r) among some surgical specialities are presented (Figure).



The correlation coefficient (r) between VAS scores and morphine amount given at the same time, permits comparison between the different surgical teams concerning the quality of acute pain management. It represents an interesting tool for internal audit, to maintain the focus on effective pain control as an important institutional clinical priority

Conclusion: We describe a reliable performance indicator of acute pain management quality assessment.

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Pain assessment: postoperative pain; VAS-scoring*Analgesics*: opioid, morphine*Quality assurance:* indicator

A.639 Variables influencing analgesia during ESWL-treatment

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A prospective study of analgosedative consumption using a PCA-device

Patients treated with the new third-generation electromagnetic lithotriptors no longer require general or regional anesthesia. However, there is need for analgosedation Demographic and pathology-specific factors may influence the consumption of these drugs, as well as the occurrence of side-effects. The aim of the study was to identify these factors

During a 7-month period, 152 calculus-treatments with the new Dornier U/50 machine were recorded (one per patient or per localisation). For each patient (ASA I–III), demographic and stone- and therapy-related data were recorded. Patients were induced with prop. 1 mg/kg and alfentanil 0 01 mg/kg When needed, they could administer themselves via PCA a bolus of prop. 0.25 mg/kg and alfentanil 0 005 mg/kg with a lock-out of 5 minutes (1) Drug-consumption and occurrence of O^2-desaturation and/or ventricular premature beats (VPB) were recorded and related to the different parameters

There is a tendency to a slightly greater need of analgesia in patients treated for distal ureteral stones compared to those with prevesical or pyelo-ureteral-junction (PUJ) localisations, although not statistically significant. ESWL-treatment for tendinitis calcarea of the shoulder needed approximately as much analgesia as PUJ-stones. Women and younger people tended to consume more alfentanil. A significantly greater consumption occurred with an increasing number of shockwaves ($p = 0.0001$) and with a greater exposed surface area of the stone ($p = 0.0037$, both S-N-K test), but not with an increasing percentage of maximum applicable energy. SaO^2 <90% was seen more often in people over the age of 60 ($p = 0.054$, 2-tailed Fisher's Exact test) and a tendency towards the same was also noted in the more obese The occurrence of VPB was significantly higher in calyx-, pyelum- and PUJ-stones than in the more distally located ($p = 0.001$ chi-square), but there was no correlation with O^2-desaturation.

Using this method of analgosedation, which was very satisfying for both patients and physicians, we were able to determine some factors indicating the need for pain control and identifying patients at risk

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ESA FREE PAPER PRIZE COMPETITION

A.242 Does PEEP induce additional alveolar recruitment when set above the lower inflection point of the pressure-volume curve?

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Background and Goal of the Study: Best PEEP is usually considered as equal to the lower inflection point (LIP) determined on the pressure volume (P-V) curve plus 2 cmH_2O (1). The goal of this study was to determine whether PEEP induces a further alveolar recruitment when set 7 cmH2O above the LIP.

Patients and Methods: 14 hypoxemic patients (age = 61 ± 13 yrs, $PaO_2 = 166 \pm 94$ mmHg; and $Qs/Qt = 40 \pm 12\%$ at $FiO_2 = 1$) were included Three conditions were tested ZEEP, PEEP = LIP + 2 cmH_2O (PEEP1 = 11 ± 1 cmH_2O) and PEEP = LIP + 7 cmH_2O (PEEP2 = 16 ± 1 cmH_2O). In each condition, hemodynamic and respiratory parameters were measured, a thoracopulmonary P-V curve was constructed and a CT scan at end expiration was performed. Lung volumes were determined from the CT scan by the frequency histogram analysis technique (2). Results are presented as mean ± SD.

Results and Discussion: PaO_2 increased by 61 ± 85% in PEEP1 and by 108 ± 120% in PEEP2 ($p < 0.05$) and Qs/Qt decreased by 16 ± 13% in PEEP1 and 28 ± 11% in PEEP2 ($p < 0.05$). The volume of non-aerated lung (CT number between −100 and +100 HU) decreased from 866 ± 419 ml in ZEEP to 739 ± 463 ml in PEEP1 and to 534 ± 286 ml in PEEP2 ($p < 0.05$) corresponding to an alveolar recruitment of 25 ± 6% and 38 ± 6%, of consolidated lung respectively ($p < 0.05$). The volume of aerated lung (CT number between −1000 and −500 HU) increased from 651 ± 723 in ZEEP to 1337 ± 1230 in PEEP1 and 1695 ± 1179 in PEEP2 ($p < 0.05$). The volume of overdistended areas (CT number between −1000 and −900 HU) increased from 11 ± 18 ml in ZEEP, to 60 ± 101 ml in PEEP1 and 151 ± 240 ml in PEEP2 ($p < 0.05$). The slope of the thoraco-pulmonary P-V curves did not change between the three conditions

Conclusions: PEEP induces a further alveolar recruitment when set largely above the LIP. This additional alveolar recruitment is associated with a slight but significant overdistension.

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A.298 Adding low-dose ketamine to general anaesthesia suppresses the serum IL-6 response after cardiopulmonary bypass

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Background and Goal of Study: Cardiopulmonary bypass (CPB) has been proposed as a model for studying the inflammatory cascade involved in the systemic inflammatory response syndrome (SIRS) SIRS seems to result from overwhelming inflammation which is caused by excessive release of cytokines. Serum interleukin-6 (IL-6) concentration appears to be a good indicator of activation of the inflammatory cascade and predicts subsequent organ dysfunction and death (1)

Opioid drugs and local anaesthetics seem to have little effect on the IL-6 response (2). Experimental data has shown that ketamine inhibits nitric oxide (NO) production via inhibition of TNF. In the present study we compared the effects of adding 0.25 mg/kg of ketamine to general anaesthesia on serum IL-6 levels during and after elective coronary artery bypass grafting (CABG)

Methods: Thirty-one patients undergoing elective CABG were randomized to one of two groups and prospectively studied in a double blind manner. The protocol for the study was approved by the local ethics committee The patients received either ketamine 0 25 mg/kg or a similar volume of normal sa'ine as an addition to high dose fentanyl anaesthesia Blood samples for analysis of serum IL-6 levels were drawn before the operation, at termination of CPB as well as at 4, 24, 48 hours following surgery and on the 3rd, 4th, 5th, 6th, 7th and 8th days postoperatively.

Results: Low-dose ketamine suppressed the serum IL-6 response immediately following CPB and at 4, 24 and 48 hours postoperatively ($p < 0.05$). During the first 7 days following surgery the serum IL-6 levels in the ketamine group were significantly lower than in the control group ($p < 0.05$). On day 8 after surgery IL-6 levels in both groups had returned to their baseline values. In this study fewer major postoperative complications were found in the ketamine group than in the control group

Conclusions: We conclude that the addition of low-dose ketamine to high dose fentanyl reduces the IL-6 response to CABG.

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A.345 Systemic haemodynamic effects ofhypertonic saline 7.2% in patients with raised intracranial pressure

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Background & Goal of Study: In spite of data suggesting a potential role for hypertonic saline solutions (HSS) in the treatment of intracranial hypertension (ICH), only a few studies have been done on humans[1,2] The goal of this study is to evaluate the effects during 2 hours produced by a 15 minute infusion of 7.2% on the ICP and systemic hemodynamics

Materials & Methods: A prospective study was carried out in 14 consecutively admitted patients with an acute head injury and raised intracranial pressure within the first 72 h after injury Each patient received an infusion of 7 2% HSS (1233 mEq/L, volume 1.5 ml/kg) during fifteen minutes when the ICP was greater than 15 mmHg Heart rate (HR), mean arterial blood pressure (MABP), cardiac index (CI), pulmonary artery occlusion pressure (PAOP), systemic vascular resistance index (SVRI), intracranial pressure (ICP), cerebral perfusion pressure (CPP) were collected before infusion of 7.2% HSS and at 5, 30, 60 and 120 minutes after the infusion (T_5, T_{30}, T_{60}, T_{120}) Core temperature was measured before infusion and at T_{120}. Urine output was measured at T_{120}. Baseline values were compared to the subsequent values using Wilcoxon rank sum text for difference. Values are given as the mean ± SD.

Results: Mean age in the group was 34 ± 16 years. The mean initial Glasgow Coma Scale equaled 7 ± 3. Mean ICP before HSS infusion equaled 26 mmHg and at T_{120} equaled 18 mmHg ($p < 0\ 001$). CPP rose significantly ($p < 0.05$) during the first hour after infusion HR increased significantly ($p < 0\ 05$) during the first thirty minutes after the infusion. There was no significant change in the MABP ($p > 0.0929$) during the study period The SVRI fell ($p \leq 0.05$) and the CI ($p < 0\ 05$) increased, both significantly during the first hour following the infusion PAOP increased ($p < 0\ 05$) five minutes after the infusion Urine output and core temperature did not change significantly.

Conclusions: The administration of 7.2% HSS decreases SVRI, expands plasma volume and increases CI. The fact that 7.2% HSS significantly decreases raised ICP without significantly decreasing MABP or significantly increasing urine output supports the idea that its administration could be more beneficial than other drugs in patients with traumatic brain injury, ICH and hypovolemia.

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A.387 Continuous lumbar plexus block: where does the catheter go?

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Background and Goal of Study: Continuous lumbar plexus block, using the anterior approach, is widely used for post operative analgesia after proximal lower limb surgery Authors claim that they have a lumbar plexus block without supporting evidence that they have succeeded in positioning the catheter in proximity to the lumbar plexus The aim of this study was to evaluate the characteristics of catheter threadings from below the inguinal ligament and the correlations between the catheter position and effective sensory and motor blockades.

Patients and Methods: After institutional approval, 86 consecutive patients scheduled for proximal lower limb surgery were enrolled. After general anesthesia, once the patients were awakened and extubated, the femoral nerve was located using a nerve stimulator and 16–20 cm of a catheter were placed in the fascial sheath of the femoral nerve. 3 ml of contrast media were injected in the catheter and a frontal pelvic region's radiograph was taken. The local anesthetic solution used for all patients was 30 ml of an equal volume mixture of 2% lidocaine with epinephrine and 0 5% bupivacaine. Sensory blockade (cold and pinprick tests) was evaluated in the three nerve territories of the thigh 30 min after injection as well as motor blockade of the femoral (F) and oturator (O) nerves Statistical comparisons were performed using the Mann-Withney test

Results: Six block failures were noted (7%) (4 catheter tips at the iliac creast, 1 catheter migration in the sartorius muscle and 1 under the abdominal muscles fascia). The tip of the catheter reached the lumbar plexus area in 19 patients (22%) and was under the fascia iliaca in 61 patients (71%). A '3 in 1' block was obtained in 90% of cases when the catheter reached the lumbar plexus and in 31% when the catheter was under the fascia iliaca ($p < 0.05$). When we compared external (over the iliacus muscle) and internal (in the psoas muscle area) subfascial catheter tip positions, '3 in 1' block was achieved in respectively 18% and 47% of the patients ($p < 0.05$), sensory blockade of the F nerve was obtained in 94% and 100%; of the O nerve in 18% and 78% ($p < 0\ 05$); of the lateral femoral cutaneous nerve in 94% and 46% ($p < 0\ 05$) of the patients.

A motor blockade of the F nerve was obtained in 84% of the patients and of the O nerve in 41% of them.

Discussion and Conclusion: During a continuous lumbar plexus block via the anterior approach, the threated catheter reached rarely the lumbar plexus area The quality of the sensory blockade of each nerve depends of the position of the catheter under the fascia iliaca.

A.589 The efficacy of intravenous regional guanethidine blockade in the treatment of post-traumatic algodystrophy

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Background: The aim of this study was to determine the efficacy of intravenous regional sympathetic blockade (1) in the early treatment of algodystrophy of the hand following Colles' fractures.

Methods: Between March 1995 and December 1996 adult patients with Colles' fractures were assessed for features of algodystrophy at nine weeks from fracture (2) Pain and finger tenderness were evaluated using verbal pain scores and dolorimetry, vasomotor instability by questionnaire, finger stiffness by finger goniometry, hand and finger swelling by water displacement and arthrocircometry and grip strength using a grip dynamometer Patients with algodystrophy were entered into a prospective, randomised, double blind trial of serial intravenous blocks with either a 15 mg guanethidine in 30 ml prilocaine or b. 30 mls normal saline Following each block patients were assessed at 24 hours, 48 hours and one week Serial blocks were administered at weekly intervals until dolorimetry ratios returned to normal or a maximum of four blocks had been administered Patients were then followed up for six months

Results: 377 patients with Colles' fractures were assessed and 82 patients identified with algodystrophy 27 patients received serial intravenous blocks containing guanethidine and prilocaine and 30 patients received serial blocks containing normal saline. There was no difference in the number of blocks administered or in the proportion of patients who responded to treatment between to the two groups No significant difference was seen in the improvement of pain, finger tenderness, finger stiffness, swelling or grip strength between the two groups. Patients treated with guanethidine had significantly worse vasomotor instability scores at 30 weeks compared with the normal saline group

Conclusion: The results of this study suggest that intravenous sympathetic blockade with guanethidine has no significant effect on pain and does not alter the natural history of algodystrophy following Colles' fracture.

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A.638 Effects of regional analgesia on long-term surgical outcome after knee surgery

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Goal of Study: Answer to the question Can an analgesic technique influence the surgical outcome of knee joint surgery?

Materials & Methods: After informed consent and IRB approval, 56 ASA class 1 or 2 patients scheduled for knee surgery (arthroplasty or arthrolysis) were randomly divided into 3 groups according to the postoperative analgesic technique. Following a standardized general anesthesia, in group A (n:19), IV-PCA morphine was used (1 mg doses, lockout interval of 7 min). Continuous femoral block (CFB) was used in group B (n 20): an initial dose of 30 ml of 2% lidocaine with 1/200 000 epinephrine was administered via a femoral catheter, followed by a 48 hours continuous infusion of 1% lidocaine + 0.03 mg/ml morphine + 2 μ/ml clonidine (rate 0.1 ml/kg/hour). Epidural analgesia (EA) was used in group C (n:17): 2 mg morphine and 10 to 15 ml of 2% lidocaine were administered in the epidural space in order to obtain a T10 spread, followed by continuous infusion as group B Daily sessions of 10 hours of continuous passive motion

(CPM) were started on day 1. The intensity of pain was assessed, twice a day during mobilization, using a visual analog scale (VAS). The maximal knee flexing obtained during CPM was compared with the targeted level prescribed by the surgeon. The maximal amplitude of knee flexion was assessed on day 5 upon hospital's discharge and at the end of the first and third months. The stay in rehabilitation center (in days) was noted. Results are expressed as median values (range). P value < 0.05 was considered significant.

Results & Discussion: There was no demographic difference between groups. The VAS values in group A were significantly higher than those of groups B and C. Groups B and C performed significantly better postoperative knee mobilization than group A [Table I]. The resulting degree of knee flexion noted on day 5 and upon discharge from the hospital, was higher for the patients of groups B and C than those of group A, but there was no significant difference on first and third month [Table II]. However, duration of rehabilitation was significantly longer in group A [50 (30–80)] than in group B [40 (21–60)] and C [37 (30–45)]. Then, regional analgesia, by providing effective pain relief during CPM, improves early rehabilitation and convalescence.

Table I Quality of early rehabilitation $^{\#}p < 0.05$ vs CFB and EA

	PCA		CFB		EA	
	D1	D2	D1	D2	D1	D2
Mobilization (% of surgeon's prescription)	$75^{\#}$ (0–100)	$80^{\#}$ (0–100)	100 (66–100)	100 (66–100)	100 (92–100)	100 (95–100)

Table II Knee flexion (degree). $^{\#}p < 0.05$ vs CFB and EA

	Day 5	Discharge	Month 1	Month 3
PCA	60 (45–80)$^{\#}$	80 (60–100)$^{\#}$	90 (80–100)	125 (90–140)
CFB	80 (55–90)	90 (60–100)	95 (90–105)	125 (95–130)
EA	85 (40–105)	90 (60–105)	105 (100–130)	130 (110–140)

Conclusion: Following major knee surgery, both CFB and EA enhance the quality of early rehabilitation and contribute for hastening of convalescence and reduction in overall hospital stay. However, regional analgesia do not improve the long term surgical outcome when compared with IV-PCA. Cost saving should be assessed.

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

75 years ago

In 1998, the *British Journal of Anaesthesia* celebrates its 75th birthday. The first issue was published in July 1923. It was followed by a second issue in October of that year, and two more in 1924; together they became volume 1 of this international journal. The first editor, from 1923–1928, was Hyman Morris Cohen, a general practitioner and anaesthetist in Manchester. Born in New York on Christmas Day, 1875, Dr Cohen underwent military training and then studied medicine at Harvard University.[1] On graduating in 1896, he served as a Surgeon Lieutenant in the Philippines, where he studied both Spanish and the native language, and compiled an English–Spanish Visayan dictionary.[2] When he returned to New York in 1904, he married Etta Rothband, a Manchunian lady. Realizing that he too had relatives in Manchester, in 1913 Cohen resigned his commission from the military and the couple came to live in the city. Somewhat surprisingly, his medical qualification was not recognized in Great Britain and so without hesitation, Cohen retrained at St Bartholomew's Hospital Medical School, London. Here he is thought first to have come under the influence of the anaesthetist, H. Edmund Boyle, who encouraged Cohen to take up the specialty. On his British graduation in 1916 at the age of 40 yr, Dr Cohen began medical practice in Withington, Manchester and was appointed honorary anaesthetist at the St Mary's Hospitals, then the name of the Manchester teaching hospitals. The idea of a journal devoted to anaesthesia was probably conceived by Cohen, Boyle and another Manchester anaesthetist, S. R. Wilson. They arranged for guarantors and for a Manchester firm of printers and publishers, Messrs. Sherratt and Hughes, to publish the journal. This firm continued to produce the journal for the next 52 yr. But the *British Journal of Anaesthesia* failed by one year to be the first anaesthetic journal in the world; *Current Researches* (now *Anesthesia and Analgesia*) was launched in the USA in 1922.

Because of ill health, Dr Cohen retired as editor of the journal in 1928, and died from heart failure while driving through the Derbyshire countryside, in 1929.[2] Dr Wilson died in the same year. Dr Joseph Blomfield, a consulting anaesthetist at St George's Hospital, London, became the second editor. Dr Blomfield was a past president of the Royal Society of Medicine, Anaesthetic Section; he had been chairman of the anaesthetic committee of the Medical Research Council and was a founder member and a future president of the Association of Anaesthetists. Dr Blomfield was to remain editor until his death almost 20 yr later in 1948.[3] By this time, after the stringencies of the Second World War, the journal was only published infrequently; each volume was thin and the quality of production was inferior. The next co-editors, E. Falkner Hill of Manchester and T. Cecil Gray of Liverpool (1948–1958), were to begin the transformation of the *British Journal of Anaesthesia* into the form we know today. The continued development of the journal has been supported vigorously by its subsequent editors: T. C. Gray, by himself (1958–1963); J. E. Riding (1963–1973); A. A. Spence (1973–1983); W. Fitch (1983–1987); and G. Smith (1987–1997).

Volume 1 of the journal now makes interesting, albeit light, reading; it is a marked contrast from its present day descendant. But nevertheless the anaesthetists of the 1920s could teach us much about clinical practice; their technical and observational skills were, probably of necessity, greater than many of us possess today. In this issue, Drury describes anaesthetic practice in that decade in detail.[4] Pharmacological enthusiasts were as commonplace as they are now, but perhaps more adventurous. There are articles in volume 1 discussing potential new inhalation agents, such as that by Langton Hewer on acetylene,[5] which was a popular agent in Germany at the end of the last century. Langton Hewer noted that this gas was odourless (although many anaesthetists thought that acetylene, in common with ethylene, smelt of garlic).[4] Acetylene produced good muscle relaxation; rapid recovery could be relied upon and it was thought to be free from "side-effects". Its explosive properties caused less concern in the days when diathermy was only just being introduced. But it is interesting that rapid induction and awakening were as attractive features of an inhalation agent then as they are today. Concern was expressed about the difficulty in preventing postoperative nausea and vomiting, which were more frequent in those days when ether, chloroform and ethyl chloride were the main potent inhalation agents in use. No satisfactory drug treatment was available. Much discussion was continuing as to whether nitrous oxide alone was a satisfactory agent. It was appreciated that, if surgical anaesthesia was to be obtained, cyanosis was almost an inevitable accompaniment of such a technique, but to many anaesthetists, this did not cause the concern it would today.[6]

Details of local anaesthetic techniques are found in volume 1. Sacral extradural anaesthesia is described by Blomfield (the future editor).[7] Convulsions were a well recognized side effect of this technique. But it was not considered that these might be caused by the toxic effect of the local anaesthetic agent, which was usually procaine. It was generally agreed, however, that the majority of patients survived this experience without any long-term sequelae! The beneficial effect of alkalinization of local anaesthetics on the intensity of block was also appreciated at that time, as was the need to use aseptic techniques to avoid irreversible neurological complications: a topic in which there has recently been much renewed interest.[8]

Anaesthetists in 1923–1924 were concerned to keep patients warm, especially during prolonged surgery, and possibly made more effort in this respect (by wrapping all four limbs in cotton wool) than we do now. "Exposure" was thought to be responsible in part for postoperative pneumonia.[9] Actually, perioperative mortality is given serious consideration in this first volume. The causes are similar to those today: postoperative pneumonia; massive haemorrhage; and cardiac arrhythmias. But the incidence was greater, in the order of 0.3%. It was thought that anaesthetic deaths were much more common in the public than in the private sector, and this was explained by the greater skill of those practising in private hospitals.[9]

A. G. Levy, a London physician who was an early exponent of internal cardiac massage, exhorts anaesthetists to attempt massage through the left pleural cavity if cardiac arrest occurs during anaesthesia. Even today, there may be a reluctance to make this vital decision in a life-threatening situation. Levy warned that cardiac massage from below the diaphragm is insufficient.[10] He was later to stress the risk of cardiac arrest during chloroform anaesthesia.[4]

Tracheal tubes were just beginning to be experimented with in 1923; perhaps this is one of the biggest contrasts from present day practice.[6 11] They were used to protect the airway when it was threatened by malignant disease or a thyroid goitre; such tubes were not developed to allow artificial ventilation. The lack of mention of a neuromuscular blocking drug, or even the need for one, is almost incredible. But undoubtedly it was appreciated at that time that straining during an abdominal procedure not only caused difficulties for the surgeon, but also increased postoperative morbidity, especially in obese patients or those with pulmonary disease. Equipment enthusiasts give descriptions of improved ether masks,[12] and discuss the questionable benefits of warming ether before administration; much doubt was expressed by Shipway about its validity.[13]

Not surprisingly with an American editor, there is a significant American contribution to the first volume; even in 1923, this was an international journal. Various remedies for treating pain during childbirth are presented from the New York lying-in hospital; most are given by the rectal route and consist of mixtures of opioids, hyoscine, ether and today's panacea, magnesium sulphate.[14] One author of these articles was a founder and first president of the American Association of Anesthesiologists, James Gwathmey. Indeed, administration of drugs or fluids by the i.v. route is scarcely mentioned, another marked contrast from present day practice.

It is heartening that some anaesthetists, even in 1923, were acutely aware of the need to teach undergraduates about anaesthesia, for a healthy recruitment to our specialty. Wesley Bourne of McGill University, Canada, describes in detail the teaching of anaesthesia to his final year medical students[15]; oh, that we had the same opportunities today! The students had anaesthesia demonstrated first in the animal laboratory, where they were taught to make basic physiological estimations, using for instance, a pneumograph to measure respiratory rate. Non-invasive arterial pressure was measured in the hind leg of dogs receiving the inhalation anaesthetics of the day at varying concentrations. Only after this experience were students allowed to enter the operating room, where they were taught the need for detailed recording of physiological variables during anaesthesia. But there is no mention of undergraduate students being examined in anaesthesia or being required to administer a minimum number of anaesthetics. McGill University has often led the way in teaching medical undergraduates: how fortunate those students were to receive such individual tuition.

The historical reviews in volume 1 are, perhaps, of the greatest interest; surely all anaesthetists will be curious about the lives of Joseph Clover and John Snow. Clover's reserved character is succinctly described by D. W. Buxton; the author believed that it was this facet, together with poor health, that prevented Clover from being a successful surgeon![16] A discussion of anaesthesia from distant times to date was given by the eminent historian, Sir D'Arcy Power (who later wrote H. M. Cohen's obituary)[2]: he points out that, in the middle ages, perioperative nausea and vomiting were even common amongst surgeons![17]

Interestingly abstracts, the loathing of many contemporary editors, appeared in significant numbers, although not just from presentations at learned societies, but also as summaries of original articles from other scientific journals; copyright legislation must not have been the threat it is today. Notices and letters concerning political matters were also common; in fact, in those days, this journal resembled an official journal of an anaesthetic society, in a way that would now be inappropriate! The need for an official association of anaesthetists is mentioned in the opening editorial.[18] Not only the Scottish Society of Anaesthetists (second to the Royal Society of Medicine, Anaesthetic Section as the oldest British anaesthetic society),[19] but also the Canadian, and American and Pacific Coast Anaesthetists, had reports on their recent meetings. Book reviews were scattered through the text but, in addition, bibliographies of recent anaesthetic literature were supplied. One unnamed author argues, in a notice, of the need for a postgraduate diploma in anaesthesia. A minimum of 6 months is thought necessary for training: 3 months at any specified hospital, followed by 3 months spent at one teaching hospital by all candidates. The University of Cambridge is recommended.

Volume 1 makes easy reading because the articles are short and anecdotal. The use of references is uncommon; statistical analysis does not exist and thus the flow of words is uninterrupted. When I borrowed it from the Liverpool Medical Institution, volume 1 had not been lent out for over 25 yr; the last date due for return was May 1, 1971. May I recommend that readers browse through it again; as well as being of enormous interest, it has many salutary lessons for us to learn.

In his opening editorial of volume 1,[18] H. M. Cohen said: "it is hoped to be able to keep abreast of the times in all that appertains to anaesthesia, and to reflect the progress our speciality (sic) is making everywhere". As the ninth editor-in-chief of this international journal, such is my task for the next 5 yr.

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British Journal of Anaesthesia 1998; **80**: 4–6

EDITORIAL II

BJA citation classics 1945–1992

It is perhaps a common fault of the British that they spend too long looking at their distinguished past rather than planning for an innovative future. Nevertheless, 1998 marks the 75th anniversary of publication of the *British Journal of Anaesthesia* and the editorial board asked the Institute for Scientific Information (ISI) to undertake a search for the 50 most cited publications from 1945 until the end of 1992. These citation classics are listed in rank order at the end of this editorial (51 publications are cited as there was a joint 50th position).

There is considerable debate about the value of citation indices. The simple assumption is that citations reflect the use of the document and its impact on the specialty. Furthermore, they are used increasingly to assess scientific performance and even as an aid to determining scientific policy. There is little doubt that authors are increasingly aware of the "ratings" of the anaesthetic journals when submitting manuscripts. Sceptics argue that citation counts provide no estimate of the quality of a publication, emphasize that there is no satisfactory theory to explain citation indices and doubt the evaluations based on them. In spite of these opposing views, I believe that the *BJA* citation classics provide a fascinating insight into the development of anaesthetic practice since 1945.

Some of my preconceived ideas about the probable content of the list had to be revised. I was surprised by the international nature of the contributions at a time when the journal did not seek deliberately a global role. Citation classics originated from the USA, Canada, Australia, South Africa, Germany, Denmark, Sweden, Finland and Israel: in total approximately one-third of manuscripts. I also expected that there would be many review articles in the citation classics. However, basic research articles predominated, although there were reviews on: the pharmacokinetics of local anaesthetic drugs (No. 9); solubility coefficients for inhaled anaesthetics (No. 14); clinical assessment of neuromuscular transmission (No. 38); benzodiazepines (No.42); and the physiology of cerebral blood flow (No. 49). Several citation classics describe the introduction of important new drugs: halothane in 1956 (No. 4); pancuronium in 1967 (No. 33); propranolol in 1967 (No. 27); diazepam in 1970 (Nos 16 and 42); Althesin in 1971 (No. 8); and atracurium in 1981 (No. 6 and 12). The importance of unpredictable adverse responses to commonly used anaesthetic agents is highlighted by the classic articles on malignant hyperthermia (Nos 2, 11 and 13), histamine release after i.v. drugs (Nos 19, 25 and 26) and nitroprusside metabolism (No. 30).

Nearly 25% of the articles describe investigations into respiratory and cardiovascular aspects of anaesthesia. This probably reflects the importance of these subjects in past decades, but it is also coincident with the observation that citation classics occur most commonly 20–25 yr after publication. It is interesting, therefore, to examine those classics which have achieved recognition over a prolonged period of time or very quickly.

Three classics were published more than 35 yr before the end of the search, that is before 1957 (Nos 4, 5 and 47). These articles describe the clinical evaluation of halothane (1956), elimination of rebreathing in various semi-closed anaesthetic systems (1954) and EEG changes produced by thiopental (1951), respectively. The citation search revealed that all three articles were quoted in 1992, and Mapleson's paper on five occasions. Indeed, the sustained contribution of Mapleson to anaesthetic research is remarkable; he last published in this journal in 1997. At the other end of the time scale, six articles achieved classic status within 12 yr of publication, 1980 or later. Two describe the pharmacology of atracurium (Nos 6 and 12) and two are concerned with the efficacy of extradural morphine (No. 7) and its complications (No. 3). The remainder are a review of the monitoring of neuromuscular transmission (No. 38) and the pharmacokinetics of fentanyl and alfentanil (No. 48). There are some obvious similarities between the old and new classics: clinical evaluation of new agents, description of the elimination of anaesthetic drugs (gases) and the novel central nervous system effects of existing drugs. The importance of extradural opioids in modern practice is mirrored by the rapid achievement of classic status of the contributions from Sweden (No. 3) and Israel (No. 7).

This list defines the top 50 cited publications at the end of 1992 and so must be considered a "snapshot" of the *BJA* literature. Changes are inevitable, and the search showed that some classics had not been cited in the past 2 yr. It was notable, however, that many publications in the top half of the list were cited frequently in 1992 (Nos 1, 3, 4, 5, 8, 9, 14, 16 and 17) and so are likely to remain classics for some time.

It was an enjoyable task to read all the manuscripts. I was struck not only by the marked changes in anaesthetic and surgical practice, but also in the design and conduct of clinical research. Gastric surgery was commonplace and used frequently as a model for upper abdominal procedures. In one study, 90% of patients were smokers (No. 36). Ethics Committees and informed consent were rarely mentioned, randomization and blinding often omitted, and when statistical analysis was undertaken it was unusual for the test to be described. Conversely, great emphasis was often placed on the accuracy and precision of the physiological measurements, and the number of patients studied was usually large (173 in No. 31 and 265 in No. 46). The articles were often lengthy, with a discussion that ranged freely around the subject and so allowed the development of further ideas. In contrast, Harrison succinctly described the successful use of dantrolene in malignant hyperthermia in five pigs in two pages (No. 13). It is probable that some of these classics would not survive rigorous assessment in 1998 and yet they represent the standard of the time, and their value to anaesthesia is beyond doubt.

The editor-in-chief has chosen 12 articles from the list of citation classics and one will be reproduced in each issue of the journal in 1998, followed by a short commentary on the importance of the work. The editorial board hope that this brief bout of nostalgia will be an interesting addition to the usual articles. The board will strive to continue to serve both readers and authors as we work towards the centenary in 2023.

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Acknowledgments

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CLINICAL INVESTIGATIONS

Comparison of continuous and intermittent administration of extradural bupivacaine for analgesia after lower abdominal surgery

L. A. DUNCAN, M. J. FRIED, A. LEE AND J. A. W. WILDSMITH

Summary

We have compared intermittent bolus and continuous infusion of extradural local anaesthetic for pain relief in a randomized, double-blind study of 48 patients who underwent major abdominal gynaecological surgery. Each patient received 5 ml of 0.375% bupivacaine hourly, either as a bolus over 5 min or as a constant infusion. Patients who received the intermittent administration technique maintained a more extensive sensory block, reported marginally better analgesia and had a lower requirement for rescue medication. The intermittent bolus technique was not associated with an increase in side effects. (*Br. J. Anaesth.* 1998; **80**: 7–10)

Keywords: analgesic techniques, extradural; anaesthetics local, bupivacaine; surgery, gynaecological

Extradural administration of local anaesthetic is now well established in the management of acute pain. Constant rate infusion from an electromechanical pump is generally used, mainly to minimize medical and nursing workload. In addition, there is a perception that constant infusion produces an unchanging block to maintain analgesia and minimize cardiovascular disturbance.[1] With constant infusions of local anaesthetic, sensory block has been shown to regress with time resulting in a requirement for supplementary analgesia,[2, 3] and even in the presence of an apparently effective extradural block there may be a need for additional medication (usually an opioid) in as many as 50% of patients.[4]

Intermittent injections of extradural local anaesthetic may provide more reliable analgesia than that obtained by continuous infusion,[5] but the lack of suitable pumps implied that this method could not be used widely. The development of devices which can deliver bolus injections at regular intervals has now made this method of administration practicable. This study was designed to compare constant infusion and intermittent injection of extradural bupivacaine after major gynaecological surgery.

Patients and methods

After obtaining approval from the area Ethics Committee and informed consent, we studied 48 ASA I, II or III patients. All were undergoing major gynaecological surgery via a lower abdominal incision and were premedicated with temazepam 10–30 mg, 1 h before operation. On arrival in the anaesthetic room a peripheral i.v. infusion of Hartmann's solution was commenced and an extradural catheter was inserted at a lower thoracic or upper lumbar spinal interspace. A test dose of 4 ml of 2% lidocaine was administered to exclude intravascular or intrathecal catheter placement and was followed by 16 ml of 2% lidocaine with epinephrine 1:200 000. General anaesthesia was induced with either thiopental 250–375 mg or propofol 100–200 mg i.v. and maintained by inhalation of either enflurane or isoflurane (1–2%) and 70% nitrous oxide in oxygen. Patients breathed spontaneously via a laryngeal mask or a tracheal tube, and succinylcholine 1 mg kg^{-1} was used to facilitate intubation if required.

At 1 h or skin closure, whichever occurred first, 0.5% bupivacaine 10 ml was injected extradurally. Patients were then allocated randomly to one of two postoperative extradural regimens. Every patient received 0.375% bupivacaine 5 ml hourly, either at a constant rate infusion (control group) or as an hourly bolus delivered at 1 ml min^{-1} (study group). A Medfusion 2001 syringe pump (Medex Medical) was used in all patients and was programmed by an anaesthetist who was not one of the investigators, all of whom were unaware of the mode of administration until the end of the study. All patients received i.v. patient-controlled analgesia from an Abbott Lifecare PCA system set to deliver a 1-mg bolus doses of morphine with a lockout time of 5 min.

As soon as the patient was able to co-operate after recovery of consciousness, the upper and lower levels of block to pinprick and the degree of motor block (Bromage scale) in the legs were assessed, together with pain (10-cm visual analogue scale (VAS)) at rest, on coughing after deep inspiration and on moving from the supine to the sitting position. These assessments were repeated 2, 4, 6, 9, 12, 21 and 24 h after surgery. At 4, 9 and 24 h, cumulative morphine consumption was recorded and patients were asked to rate pain control to date using a four-point verbal rating scale (VRS: 1 = poor, 2 = fair, 3 = good, 4 = excellent). Routine measurements of heart rate, arterial pressure, ventilatory frequency (hourly) and volume of extradural solution infused were carried

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Table 1 Patient details (mean (SD or range) or number)

	Bupivacaine 0.375% intermittently (n=19)	Bupivacaine 0.375% continuously (n=21)
Age (yr)	43.5 (21–66)	45.9 (29–85)
Weight (kg)	67.9 (13 7)	63.9 (9.9)
Height (cm)	163.5 (6 3)	161.6 (6 3)
ASA (I/II/III)	12/5/2	13/7/1
Extradural site		
T10–11	7	3
T11–12	9	15
T12–L1	3	2
L2–L3		1
Incision		
Transverse	16	17
Mid-line	3	4
Duration of surgery (min)	60.7 (20.3)	53 6 (14.4)

Table 2 Requirements for rescue medication. Morphine consumption is shown as median (interquartile range). Extradural top-ups were of 0.5% bupivacaine as a 5-ml bolus dose

		Time		
		0–4 h	4–9 h	9–24 h
Morphine consumption (mg)	Intermittent group	4 (0–9)	4 (2–6)	11 (4–14)
	Continuous group	3 (1–6)	6 (3–10)	12 (6–15)
No. of extradural top ups	Intermittent group	1 in 1 patient	1 in 1 patient	1 in 1 patient
	Continuous group	3 in 3 patients	6 in 4 patients	10 in 4 patients

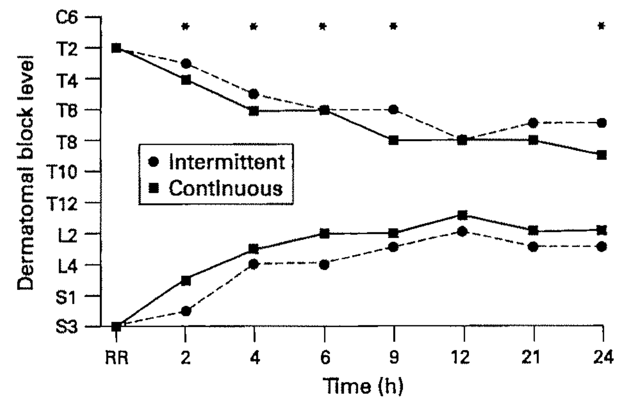

Figure 1 Upper and lower level of block to pinprick in the intermittent bolus and continuous infusion groups (median). *$P < 0.05$ between groups.

out by the nursing staff according to normal ward practice.

Comparisons between groups were made using chi-square and Mann–Whitney with Bonferroni correction tests, as appropriate.

Results

Eight patients were excluded from the study, two as a result of technical problems with either the extradural or the infusion pump, and six as a result of design violations by the ward nursing staff. In patients who completed the study, there were minimal differences between the two groups in patient characteristics, level of extradural catheter insertion, type of incision and duration of surgery (table 1). At the first assessment after surgery there were no differences between groups in the degree of sensory or motor block, but those patients who received intermittent boluses had, as a group, more extensive sensory (pinprick) blocks thereafter. The difference was significant at 2, 4, 6, 9 and 24 h (fig. 1), but there was no difference in the degree of motor block at any time (fig. 2).

An obviously unilateral block developed in two patients in the intermittent bolus group and five in the continuous infusion group. Three patients in the intermittent group (including one with a unilateral block) received a single bolus injection of 0.5% bupivacaine 5 ml because of poor analgesia. In the continuous group, six such patients (including one with unilateral block) required a total of 19 single bolus injections for breakthrough pain (table 2). Unilateral blocks were treated only if pain relief was poor. Mean bupivacaine consumption for the 24-h study period was 456 mg in the intermittent bolus group and 473 mg in the infusion group ($P < 0.001$). Morphine consumption tended to be lower in the group receiving intermittent bolus administration, but the difference was not significant (table 2).

Both VRS and VAS results (figs 3–5) suggested that the quality of analgesia was somewhat better in the intermittent bolus group. If a VRS score of good or excellent is taken as satisfactory then 74%, 89% and 84% of patients in the intermittent group had acceptable pain relief at 4, 9 and 24 h compared with 55%, 71% and 67% of patients in the continuous group. The difference between the groups in VRS was significant at 24 h ($P = 0.05$). VAS results at rest and during movement were significantly better in the intermittent group at 4 and 6 h, but there was no difference in pain during coughing at any time (figs 4 and 5).

There were no differences in cardiovascular variables between the groups, and there were no episodes of hypotension requiring treatment in any patient.

Discussion

Extradural administration of local anaesthetic drugs provides useful analgesia after surgery, but supplementary analgesia (usually an opioid) is often required.[6] This study confirms these findings, with patients in both groups reporting low pain scores while consuming moderate amounts of morphine. Median VAS pain scores were less than 30 mm in the intermittent group at all times and, although higher, were still satisfactory in the continuous group. Patient satisfaction was assessed using a four-point VRS and was greater in the intermittent bolus group (fig. 3).

Previous investigators have suggested that continuous extradural local anaesthetic infusion is associated with less hypotension, less motor block and uninterrupted analgesia compared with intermittent bolus injection.[7] Similar results have been obtained when extradural block was used to provide analgesia in labour.[8] However, in those studies the bolus injection was administered only when the patient had developed pain and requested relief. The advantage of constant infusion techniques is that the level of block does not change acutely and the aim of this study was to see if a similarly constant block could be produced by intermittent, but regular, bolus injection. In a previous study, Scott, Schweitzer and Thorn found that this method of extradural local anaesthetic injection produced more predictable analgesia than continuous infusion without any increase in side effects.[5] However, the injections were made by nursing staff and it was not always possible to give them frequently enough to maintain analgesia.

In this study a modern electromechanical pump was used to deliver regular hourly bolus doses of bupivacaine and the findings confirm those of the earlier study. Heart rate and arterial pressure were recorded hourly by the ward staff and there was no cause for concern with either intermittent or continuous injection. However, these were relatively healthy patients who were assessed by routine clinical methods after straightforward lower abdominal surgery. A more definitive comparison of the cardiovascular effects of the two modes of extradural administration is in progress in older patients undergoing upper abdominal surgery.

In both groups the sensory level of analgesia regressed progressively during the first 6 h after operation and then remained relatively stable, a feature of continuous extradural block noted previously.[2 9 10] The initial regression has been ascribed to either tachyphylaxis or changes in local blood flow altering the uptake of local anaesthetic, but it is most likely that this represents regression of the larger bolus doses used for surgery. The block remained more extensive in the intermittent group and this is consistent with the latter interpretation.

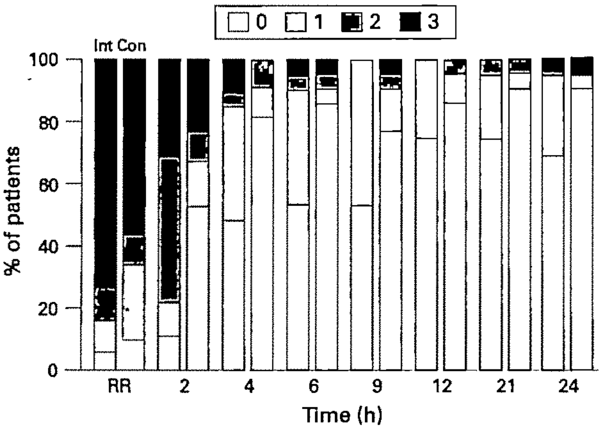

Figure 2 Degree of motor block (Bromage scale) in the intermittent bolus (Int.) and continuous infusion (Con.) groups. Most dense block recorded when motor block differed between legs. RR = Recovery room.

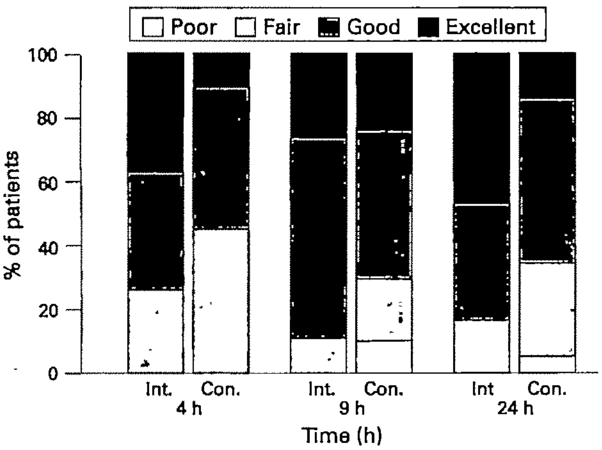

Figure 3 Verbal rating score (VRS) of overall satisfaction with pain control in the intermittent bolus (Int.) and continuous infusion (Con.) groups.

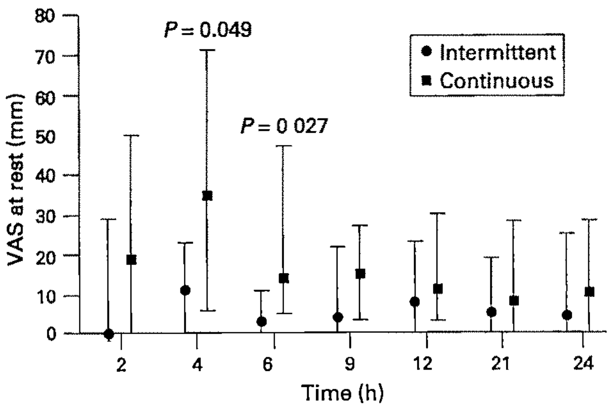

Figure 4 Visual analogue scores (VAS) at rest (median, interquartile range) in the intermittent bolus and continuous infusion groups.

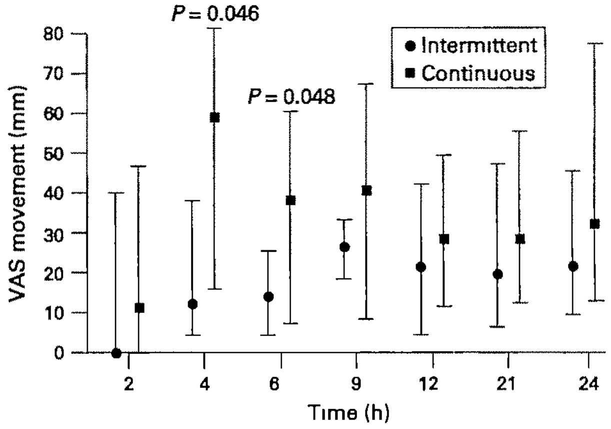

Figure 5 Visual analogue scores (VAS) on movement (median, interquartile range) in the intermittent bolus and continuous infusion groups

The faster bolus injection may create a higher pressure in the extradural space and cause the solution to spread further. In contrast, a low volume continuous infusion may be less likely to spread far from the extradural catheter, so that regression of block is more likely.

All patients in the study received opioid analgesia in addition to extradural local anaesthetic. This was by i.v. PCA, although there may be advantage in administering the opioid extradurally with the local anaesthetic.[11] One of the advantages claimed for mixtures is that reduced local anaesthetic dosage decreases the incidence of lower limb motor block. However, lower limb paralysis was minimal by 4 h in both groups (fig. 2), perhaps reflecting the level of catheter insertion as much as local anaesthetic dose. Motor block may be more of a problem with continuous lumbar extradural block after lower limb surgery.

The addition of opioid to an extradural infusion also carries the risk of producing profound respiratory depression and the underlying theme of this project was to see if modification of the technique of administration produces better quality analgesia with local anaesthetic alone, and so minimize the need for opioid supplementation. PCA with morphine was used primarily to provide another method of comparing the effectiveness of the two techniques. The supervision of both extradural and PCA infusion pumps caused no practical problems, although it may be difficult to provide both in the routine clinical setting. This is one of the reasons for trying to minimize opioid requirements by developing the method of extradural injection.

It may seem surprising that there was little difference between the groups in morphine consumption, despite lower pain scores and better patient satisfaction with the intermittent technique, but there are two possible explanations. First, a recent study has cast doubt on the reliability of PCA as an assessment technique, noting that patients use it for reasons other than pain relief.[12] Second, the aim was to provide good analgesia for all patients in the study. As a result, several patients in pain, despite the use of PCA, received supplementary bolus injections of bupivacaine from investigators who did not know which method was in use. Nineteen such injections were administered to those in the continuous group, in comparison with only three to the intermittent group and this almost certainly masked any potential increase in morphine requirement in the continuous group. An increased local anaesthetic requirement has also been shown when continuous infusion is compared with intermittent injection by patient-controlled extradural analgesia in labour.[13]

We conclude that regular, intermittent extradural administration of local anaesthetic provided better quality analgesia after surgery and reduced the need for supplementary medication compared with constant infusion of local anaesthetic. This study only compared two specific injection techniques and a wide range of combinations of volume, drug concentration and infusion rate is possible. However, the results suggest that a reappraisal of intermittent injection techniques for extradural analgesia using modern devices to ensure fixed time intervals of administration is merited. Variations in the volume, concentration and time interval of injection might reduce further the need for supplementary medication and for a separate PCA device.

Acknowledgement

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British Journal of Anaesthesia 1998; **80**: 11–13

Minimum local analgesic concentration of extradural bupivacaine increases with progression of labour

G. Capogna, D. Celleno, G. Lyons, M. Columb and P. Fusco

Summary

We have used the technique of double-blind sequential allocation to quantify the minimum local analgesic concentration (MLAC) of extradural bupivacaine for women in early (median cervical dilatation 2 cm) and late (median cervical dilatation 5 cm) labour. The first bolus was 20 ml of the bupivacaine test solution. The concentration was determined by the response of the previous woman to a higher or lower concentration of bupivacaine according to up and down sequential allocation. Efficacy was assessed using a 100-mm visual analogue pain score (VAPS). The test solution had to achieve a VAPS of 10 mm or less to be judged effective. In early labour, the MLAC of bupivacaine was 0.048% w/v (95% confidence intervals (CI) 0.037–0.058% w/v), and 0.140% w/v (95% CI 0.132–0.150% w/v) in the late group. The MLAC of bupivacaine in late labour was greater by a factor of 2.9 (95% CI 2.7–3.2) compared with the MLAC in early labour ($P < 0.0001$, 95% CI difference 0.08–0.11). We conclude that advancing labour requires an increased concentration of extradural bupivacaine for pain relief. (*Br. J. Anaesth.* 1998; **80**: 11–13)

Keywords: pregnancy; analgesia, obstetric; analgesic techniques, extradural, anaesthetics local, bupivacaine

Bupivacaine is used widely to provide extradural pain relief in labour in a wide range of doses, concentrations and volumes. The paucity of data on the dose–response relationships of extradural analgesics in labour has led to the development of a benchmark for extradural local anaesthetics, the minimum local analgesic concentration (MLAC). This is defined as the effective concentration in 50% of women in the first stage of labour (EC_{50}).[1]

The impact of advancing cervical dilatation on the MLAC has never been assessed, and we sought to take advantage of differing obstetric policies within a single maternity unit. Because one obstetric team discouraged extradural pain relief in early labour, two groups of women, one in early labour and one in late labour with minimal overlap with regard to cervical dilatation, were created. Our aim was to measure and compare the MLAC of bupivacaine at different stages of labour in these two groups of women.

Patients and methods

Our hospital Ethics Committee approved this double-blind sequential allocation study. After obtaining informed consent, we studied 61 women, ASA I or II, with singleton pregnancies and vertex presentation, requesting extradural pain relief in the first stage of labour. We excluded women who had received opioid or sedative drugs. Use of transcutaneous electrical nerve stimulators and Entonox before extradural request was not regarded as a need to exclude.

The extradural technique was standardized. I.v. Ringer's solution was infused via a forearm cannula. The extradural space was found, either at L2–3 or L3–4 interspace, in the sitting position. Loss of resistance to saline was used to identify the extradural space, limiting the injection to 2 ml in order to minimize dilution of local anaesthetic. The extradural catheter was advanced 3 cm into the space and then aspirated. For the purpose of the study, the test dose was omitted.

The first administration of bupivacaine was from a freshly prepared syringe containing 20 ml of test solution given over 5 min; bupivacaine was diluted with 0.9% w/v saline to achieve the desired concentration at room temperature.

We recruited two groups of 30 women each. Each group was comprised of women from a single obstetric team, one in early and one in late labour, creating two groups with different ranges of cervical dilatation at the time of extradural insertion. The diagnosis of labour was confirmed by the obstetric team before extradural request. Entry into the study required an initial visual analogue pain score (VAPS) greater than 30 mm.

The first woman in each group received 0.1% w/v bupivacaine, in common with the starting point of an earlier study.[2] Thereafter, the concentration of the test solution in each individual syringe was determined by the response of the previous patient to the higher or lower concentration in her test syringe, according to up and down sequential allocation. Maternal pulse, arterial pressure, frequency of contractions and fetal heart rate were monitored.

ASSESSMENT

Efficacy of the first dose was assessed using a 100-mm VAPS. The side presented to the woman in labour portrayed faces depicting happiness (0) to misery (100) in five stages. A movable cursor

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Table 1 Patient characteristics (mean (SD)), median (interquartile range) or number). Women in late labour had greater dilatation of the cervix (P<0.0001) and higher initial visual analogue pain scores (VAPS) (P<0.0001) than those in early labour

	Early (n=30)	Late (n=30)
Age (yr) (mean (range))	28.2 (22–35)	29.3 (23–38)
Weight (kg)	75.5(6.53)	74 1(6.95)
Height (cm)	166.4(4.20)	168.3(4.95)
Gestation (weeks)	40 (40–41)	40 (40–41)
Nulliparous	23	25
Multiparous	7	5
Oxytocin	8	12
Cervix (cm)	2 (2–3)	5 (5–5)
Initial VAPS (cm)	68 (59–70)	90 (85–94)

provided a numerical selection on the rear of the scale. Observations were made at 0, 15, 30 and 60 min after injection of the first bolus containing study solution. Three outcomes were possible.

Effective

This required that the VAPS decreased to 10 mm or less at the height of contraction, within 60 min, and indicated the end of the study and directed a decrement of 0.01% w/v bupivacaine for the next woman.

Ineffective

This followed failure of the VAPS to reach 10 mm within 60 min of the test solution. If at 30 min the woman claimed satisfactory analgesia despite not reaching the VAPS target of 10 mm, the study period was extended to a possible maximum of 60 min. At 30 min, after failing to reach the VAPS target, rescue analgesia consisting of 0.25% w/v bupivacaine 12 ml was offered. After this, a reduction in VAPS to 10 mm or less indicated the end of the study and directed a 0.01% w/v bupivacaine increment for the next woman.

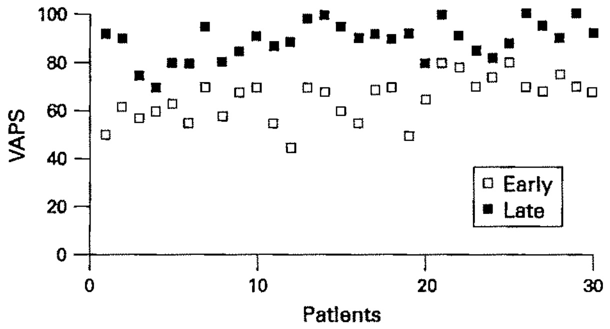

Figure 1 Visual analogue pain scores (VAPS) before extradural analgesia in the early and late groups. Median values (interquartile range) were significantly lower in the early labour group (68 (59–70) vs 90 (85–94); P<0.0001).

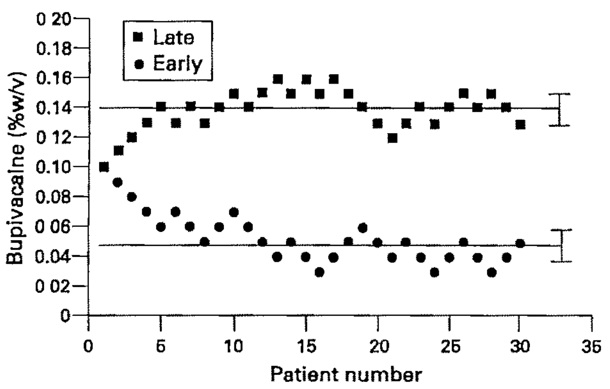

Figure 2 Minimum local anaesthetic concentration (MLAC) of bupivacaine in early and late labour, as determined by the technique of up–down sequential allocation. In the early labour group, the MLAC of bupivacaine was 0.048% w/v (95% CI 0.037–0.058% w/v) and in the late labour group, 0.141% w/v (95% CI 0.132–0.150% w/v) (P < 0.0001).

Repeat

Failure to achieve a VAPS of 10 mm after the rescue bolus implied a technical failure, and directed that the same concentration be repeated for the next woman.

For all women, age, weight, height, gestation, parity, cervical dilatation and use of oxytocin were recorded.

STATISTICAL ANALYSIS

Patient and obstetric data were collected and are presented as mean (SD) and median (interquartile range) as appropriate. The median effective concentration was estimated from the up–down sequences using the formula of Dixon and Massey which enabled MLAC with 95% confidence interval to be derived.[3] The data were also subjected to Wilcoxon and Litchfield probit regression analysis as a back-up sensitivity test. Further analyses included Student's t test, Mann–Whitney U test, Kolmogorov–Smirnoff test for Gaussian distribution and Fisher's exact test.[4 5] All analyses were carried out on two personal computers (Dell Dimension XPS P100c and Zenith Z-Star EX 486DX 50) using the following software: Microsoft Excel 6.0a for Windows, Statistical Package for the Social Sciences (SPSS) 6.1 for Windows, GraphPad Instat 2.05a for DOS and Pharmacologic Calculation System (PCS) 4.2 for DOS. Statistical significance was defined for an overall α error at the 0.05 level. All P values were two-sided.

Results

There were no significant differences in characteristics in the groups (table 1).

Women in late labour had greater cervical dilatation (median 5 (interquartile range 5–5) cm) than those in early labour (2 (2–3) cm) (P < 0.0001).

The first VAPS recorded in women in early labour (median 68) were significantly lower (P < 0.0001) than those recorded in late labour (median 90) (fig. 1).

One woman in late labour had unilateral pain that did not respond to the rescue bolus. This concentration was repeated for the next patient. The sequences of effective and ineffective analgesia are shown in figure 2.

The MLAC of bupivacaine in early labour was 0.048% w/v (95% CI 0.037–0.058% w/v) using the formula of Dixon and Massey, and 0.046% w/v (95% CI 0.038–0.056% w/v) by probit regression. The MLAC of bupivacaine in late labour were 0.141% w/v (95% CI 0.132–0.150% w/v) and 0.140% w/v (95% CI 0.132–0.149% w/v), respectively. This difference was significant (P < 0.0001, 95% CI difference 0.08–0.11). The MLAC of bupivacaine in late labour was significantly greater than that in early labour by a factor of 2.9 (95% CI 2.7–3.2).

Discussion

We have shown that the MLAC of bupivacaine increased with advancing labour. This implies that when low concentrations of local anaesthetic are used for extradural analgesia in order to achieve motor sparing and perhaps ambulation, the concentration may need to be increased as labour progresses to maintain satisfactory analgesia. Breen and colleagues reported that approximately 50% of women receiving an infusion of 0.04% w/v bupivacaine in combination with fentanyl 1.7 μg ml^{-1} and epinephrine 1.7 μg ml^{-1} went on to deliver without a change in regimen.[6]

The application of the two obstetric policies was not exact, and there was a minor degree of overlap with regard to cervical dilatation. One woman in late labour had a cervical dilatation of 3 cm; without this the two groups would have been distinct. The double difficulties posed by differing obstetric policies and consumer choice prevented randomization to the groups.

There was a significant difference in the two groups regarding the initial VAPS. This suggests that the obstetric policy was effectively applied to women in late labour who might otherwise have received extradural pain relief earlier.

The use of saline to detect loss of resistance implied that dilution of the test concentration of bupivacaine could have occurred within the extradural space. To minimize this, extradural injection of saline was reduced to a clinically insignificant volume. The alternative to saline would have been air. This was rejected because of a suggestion that pockets of air in the extradural space might obstruct the spread of local anaesthetic.[7]

The role of concentration of local anaesthetic in conduction block is in the production of differential nerve block.[8] The requirement for an increasing concentration as labour progresses prompts speculation that larger fibres are recruited as the cervix opens and the head descends. The term *visceral* is used to describe the pain of the contracting uterus and the dilating cervix, supplied by sympathetic afferent fibres, which characterizes the first stage of labour. As the presenting part distends and compresses pelvic structures during the second stage, the pain is described as *somatic.*[9] In reality the distinction between the two is not always clear cut, but it might be reasonable to speculate that at the earliest moment of labour, pain is purely *visceral* in nature. It might also be worth speculating that first stage pain is predominantly C fibre, with an increasing contribution from Aδ fibres as labour progresses. Our knowledge of spinal opioids, which block C-fibre discharge more effectively than Aδ fibres, and are more useful in the first than in the second stage of labour, supports this hypothesis.[10] [11] Such a hypothesis might explain our findings. An alternative explanation is that increasing concentration is required as the frequency of stimulation of individual pain fibres intensifies. This would be unlikely if frequency dependent block occurs in clinical practice. Studies with bupivacaine indicate that increased frequency of stimulation leads to more profound conduction block.[12]

In summary, we found that as labour progressed, there was a significant increase in the requirements for extradural bupivacaine.

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Risk factors for cardiovascular death after elective surgery under general anaesthesia

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Summary

A large epidemiological data set was used to identify 115 patients who died from a cardiovascular cause within 30 days of elective surgery under general anaesthesia. For each patient, a control was identified, matched for age (within 5 yr of the patient), sex, operation and consultant. Patients and controls were compared for cardiovascular risk factors in a matched analysis using conditional logistic regression, and a prognostic model was generated. Three risk factors were included in the final model: previous myocardial infarction (odds ratio 3.18 (95% confidence intervals (CI) 1.22–8.28), *P* = 0.018), history of hypertension (odds ratio 1.90 (0.99–3.62), *P* = 0.047) and renal failure (odds ratio 3.56 (1.04–12.10), *P* = 0.043). (*Br. J. Anaesth.* 1998; **80**: 14–19)

Keywords: anaesthesia, general; complications, death; complications, cardiovascular disease; anaesthesia, audit; records, anaesthesia

It is widely accepted that patients suffering from cardiovascular disease represent a particular challenge for the anaesthetist. With modern anaesthesia and perioperative care, major cardiovascular complications after anaesthesia and surgery are uncommon. Forrest and co-workers[1 2] reported 19 deaths and 23 myocardial infarctions in a population of 17 201 patients who underwent surgery under general anaesthesia. However, cardiovascular complication rates of 2–6% occur not infrequently in extant reports.[3–5] Such complications result from the intervention of anaesthesia and surgery rather than from any underlying disease, and even a relatively low complication rate is a cause for concern.

Study of the perioperative risk associated with cardiovascular illness is difficult. Most studies of cardiovascular risk factors and perioperative cardiovascular complications have been prospective or retrospective cohort studies.[3 5–11] The relatively low frequency of complications implies that such studies have to include a large number of patients in order to achieve adequate statistical power. An alternative approach is that of the case-control study. This study design is particularly useful for studying rare outcomes and for examining several risk factors simultaneously. Because most of the available studies are cohort studies it could be argued that they may be subject to some form of systematic bias. A case-control study which achieved similar results to the cohort studies would add weight to the validity of findings from each type of study.

We have used the Oxford Record Linkage Study (ORLS), which is a large epidemiological data set, to conduct a case-control study of risk factors for cardiovascular death after elective surgery under general anaesthesia.

Analysis of a subset of the data taken from the ORLS has been undertaken previously to examine the effects of admission arterial pressure and diagnosed hypertension on cause of death.[12] In this article some of these patients have been included together with more patients from the same data set, but all have been re-analysed with regard to this extended list of variables that we have included in our analysis. Overall, we have included 75 patients from the previous dataset, with 40 additional patients.

Patients and methods

DATA COLLECTION

The Oxford Record Linkage Study (ORLS) covers approximately 1.9 million people within the former Oxford Regional Health Authority area. It includes routine data on all hospital admissions for individuals treated within the study area. All stays in hospital, both by in-patients and day cases, are recorded and entered in the database. Patient characteristics and diagnostic data are recorded. All operations are noted and coded. Hospital records are linked to death certificates. For the current study we obtained data on patients who underwent surgery between 1979 and 1990. Patients studied underwent surgery at one of three hospitals in Oxford, or at hospitals in Banbury or Kettering. The choice of hospitals was determined by the availability of case notes in medical records departments for detailed study. The overall population of the study area was approximately 800 000. In the years covered by the study, the SMRs for circulatory disease in general and for ischaemic heart disease in particular were both approximately 88 for men and 93 for women in 1979 and were in the mid-80s for both men and women by 1990.

The ORLS was analysed to identify patients who died within 30 days of anaesthesia and surgery and

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whose death certificates included ICD9 codes (9th International Classification of Diseases) in the range 401–438 inclusive, at any position on the death certificate. The diseases covered by these codes are hypertensive disease (401–405), ischaemic heart disease (410–414), diseases of the pulmonary circulation (415–417), other forms of heart disease (420–429) and cerebrovascular disease (430–438). Patients who died after a pulmonary embolism (code 415.1) were excluded, as were those undergoing cardiac or neurosurgery. It was recognized that there are specific codes available within ICD9 for complications associated with anaesthesia (e.g. 995.4 for shock as a result of anaesthesia). These codes had not been used as certified causes of death on death certificates for any patient in the study population.

CONTROLS

For each patient at least one control was identified. Where possible two controls were identified to allow for the possible non-availability of the medical records of the first control examined. Controls were matched with patients on the following criteria:

- underwent the same operation as the patient,
- under the care of the same consultant as the patient,
- age within 5 yr of the patient,
- same sex as the patient.

When two controls were obtained, one was chosen at random and the notes obtained. If these were unavailable or if the control was excluded for any reason, the notes of the second control were examined.

EXAMINATION OF MEDICAL RECORDS

The medical records of patients and controls were obtained. As required by the local Ethics Committee, we obtained consent to examine the medical records from the consultant caring for each patient during admission for surgery. Where the consultant had died or retired, consent of his or her successor was obtained. The notes were examined in detail by a research nurse. Whenever possible, it was confirmed from the notes that the cause of death given on the death certificate was supported by the medical records. If a patient had clearly not died from a cardiovascular cause, he or she was excluded from the study. Patient data and data on cardiovascular risk factors were collected.

EXPOSURES OR RISK FACTORS

Data were collected on the following risk factors.1

Treated hypertension, angina and heart failure0

A patient was defined as having one or more of these conditions if they had been receiving medication for the condition in question. This was felt to be more reliable than depending on these diagnoses being mentioned in the notes as there was likely to be considerable variation between subjects as to whether systematic enquiry had been made for co-morbidity and as to whether this information was recorded. Drug history is recorded more consistently and can usually be corroborated from drug charts filed in the notes.

Where the term hypertension is used in this article, it refers to treated hypertension. It is important to note that this definition of hypertension was independent of admission arterial pressure.

Previous myocardial infarction, previous cerebrovascular accident, diabetes mellitus, peripheral vascular disease

Patients were considered to have one or more of these conditions if the medical records indicated this to be the case. For these conditions we believed that we could not rely on treatment history to indicate disease. Patients who have suffered a significant myocardial infarction or have peripheral vascular disease may not be receiving cardiovascular medications. Diabetes controlled with diet alone may cause significant end-organ damage.

Renal failure

Patients were said to have renal failure if they had a creatinine concentration >150 μmol litre^{-1} at admission for surgery.

DATA HANDLING

A computer database written using Microsoft Access 2.0 was used to store and examine the data. Microsoft Excel 5.0 was used to examine the tables produced by Access. Statistical analysis was performed using Stata version 4.0. Data were exchanged between the various programs using DBMScopy version 5.10.

STRATEGY OF ANALYSIS

Data were examined for errors and inconsistencies and descriptive statistics produced. Crude odds ratios were calculated and the data were examined using McNemar's test. Where one of the cells in the contingency table had a zero value, exact probabilities were calculated. Because the age difference within pairs could be up to 5 yr, there was potential for residual confounding by age within pairs. It was found that this was best adjusted for by including in the analysis each subject's deviation from the mean age of that matched pair. Adjustment for age difference within pairs was made using conditional logistic regression and these adjusted odds ratios are reported for each risk factor.

Multivariate analysis was performed using conditional logistic regression, the strata being identified by pair numbers linking the patients and matched controls. The aim was to produce a prognostic equation for perioperative cardiovascular death. Terms which were statistically significant at the 0.05 level using the log likelihood test were included in the final regression equation. We also report the result of the Wald test for each term in the final equation. This test is based on a normal approximation to the log likelihood. Terms which were significant on log likelihood testing were included in the final model, even if not quite significant at the 0.05 level by the Wald test.

Table 1 Results for individual risk factors. Concordant and discordant pairs

	No. of pairs			
	Case exposed/ control unexposed	Case unexposed/ control exposed	Case exposed/ control exposed	Case unexposed/ control unexposed
Myocardial infarction	25	6	5	79
Angina	24	7	3	81
Hypertension	39	16	15	45
Renal failure	18	4	0	93
Heart failure	24	9	1	81
Peripheral vascular disease	10	4	18	83
Cerebrovascular accident	13	6	0	96
Diabetes mellitus	13	14	2	86

As with the analysis for individual risk factors, a term for deviation of each subject from the mean age of that pair was included in the model. It was not possible to examine the main effects of exposures on which the subjects had been matched, that is age, sex, type of surgery and consultant. However, interactions between these exposures and hypertension were examined. Potential interactions between the various risk factors were also examined.

Results

We identified 177 patients who died from a cardiovascular cause within 30 days of elective surgery under general anaesthesia; 115 of these patients were selected for further study, together with the same number of individually matched controls. Thirty-seven patients were excluded because the notes of either the patient or the control, or both, were missing. Twenty-five patients were excluded because no matching control could be identified.

Mean age of the patients was 72.6 (range 45–93) yr and that of the controls 71.3 (43–90) yr. Mean age difference between the patients and controls was 0.63 (SD 1.82) yr. Pairs were matched for sex. In 74 (64%) of the pairs the patient and control were male.

Patients and controls were matched for operation. In 29 (25%) pairs, the patient and control underwent abdominal surgery, in 11 (10%) vascular surgery, in 12 (10%) hip replacement surgery and in 63 (55%) pairs other surgery. The other surgery group included patients undergoing endoscopic procedures, including TURP and cystoscopy, in addition to operations such as inguinal hernia repair and Keller's procedure.

Among the patients the mean time from operation to death was 8.4 days (median 6 days). Seventy-eight (68%) of the patients died of myocardial infarction or ischaemic heart disease, 23 (20%) died of heart failure and in 14 (12%) patients the cause of death was cerebrovascular accident. The number of concordant and discordant pairs for each risk factor is shown in table 1.

RISK ASSOCIATED WITH INDIVIDUAL RISK FACTORS

The crude odds ratios for perioperative cardiovascular death are reported for each risk factor in table 2. Table 2 also gives the odds ratios adjusted for residual confounding by age. After adjustment for residual confounding by age, histories of myocardial infarction, angina, hypertension, renal failure and heart failure were observed to have a significant effect on the risk of perioperative cardiovascular death. The odds ratio associated with a history of myocardial infarction was 4.04 (95% confidence intervals (CI) 1.60–10.19; P = 0.003). The odds ratio associated with a history of angina was 3.55 (1.48–8.82; P = 0.004). For a history of treated hypertension the odds ratio was 2.53 (1.38–4.69; P = 0.003). The odds ratio associated with renal failure, defined as a serum creatinine concentration >150 µmol litre^{-1}, was 4.23 (1.36–13.20; P = 0.013). For a history of heart failure requiring medical treatment the odds ratio was 2.80 (1.23–6.41; P = 0.014). The odds ratios for a history of peripheral vascular disease, cerebrovascular accident or diabetes mellitus were not statistically significant.

CONDITIONAL LOGISTIC REGRESSION

The data were then examined by forward stepwise conditional logistic regression. The final model is reported in table 3.

In the final regression model two risk factors (myocardial infarction and renal failure) were significant at the 0.05 level, and hypertension reached borderline significance at this level. The coefficient adjusting for residual confounding by age was also significant at the 0.05 level and its inclusion had a significant impact on the values of the other regression coefficients. No significant interaction terms were identified.

The coefficient for myocardial infarction in this equation was 1.16 (SEM 0.49), giving an odds ratio of 3.18 (95% CI 1.22–8.28) and a P value of 0.018 by the Wald test. The coefficient for hypertension was 0.64 (SEM 0.33), giving an odds ratio of 1.90 (95% CI 1.00–3.62). The Wald test for the effect of

Table 2 Results for individual risk factors. Crude and age-adjusted odds ratios

	Crude odds ratio		Age-adjusted odds ratio	
	Odds ratio (exact 95% CI)	Chi-square(1 df) P value	Odds ratio (exact 95% CI)	z (Wald test) P value
Myocardial infarction	4.17 (1.67–12.43)	11.65 P=0.0006	4.04 (1.60–10.19)	2.96 P=0.003
Angina	3.43 (1.43–9.42)	9.32 P=0.0023	3.55 (1.48–8.52)	2.84 P=0.004
Hypertension	2.44 (1.33–4.68)	9.62 P=0.0019	2.53 (1.38–4.69)	3.00 P=0.003
Renal failure	4.5 (1.48–18.29)	8.91 P=0.0028	4.23 (1.36–13.20)	2.49 P=0.013
Heart failure	2.67 (1.20–6.51)	6.82 P=0.009	2.80 (1.23–6.41)	2.45 P=0.014
Peripheral vascular disease	2.5 (0.72–10.95)	2.57 P=0.1088	3.01 (0.84–10.80)	1.69 P=0.91
Cerebrovascular accident	2.67 (0.77–6.95)	2.58 P=0.1083	2.42 (0.86–6.85)	1.67 P=0.94
Diabetes mellitus	0.93 (0.40–2.13)	0.04 P=0.85	0.89 (0.40–2.00)	0.28 P=0.78

Table 3 Final conditional logistic regression model for risk factors for cardiovascular death after anaesthesia and surgery

	Regression coefficient (SEM)	Odds ratio (95% CI)	Chi-square (comparison of likelihoods)	*P* value (comparison of likelihoods)	*z* (Wald test)	*P* value (Wald test)
Myocardial infarction	1.16 (0.49)	3.18 (1.22–8.28)	6.50 1 df	0.011	2.37	0.018
Hypertension	0.64 (0.33)	1.90 (1.00–3.62)	3.95 1 df	0.047	1.95	0.052
Renal failure	1.27 (0.63)	3.56 (1.04–12.18)	4.75 1 df	0.029	2.02	0.043
Age difference	−0.19 (0.06)	0.83 (0.73–0.93)	10.1 1 df	0.0015	2.96	0.003

hypertension was not quite significant at the 0.05 level ($z = 1.95$, $P = 0.052$). The Wald test is based on the normal approximation to the log likelihood. A comparison of the log likelihoods associated with models including and excluding hypertension (log likelihood ratio test) yielded a value of chi-square = 3.95, P=0.047, 1 df. Hypertension was therefore retained in the model.

The coefficient for renal failure was 1.27 (SEM 0.63). This translated to an odds ratio for renal failure of 3.56 (95% CI 1.04–12.18). The Wald test for the coefficient for renal failure was significant at the 0.05 level ($z = 2.02$, $P = 0.043$).

Discussion

FINDINGS

When adjustment was made for residual confounding by age, but not for other confounding factors, five risk factors were found to be significantly associated with cardiovascular death within 30 days of anaesthesia and surgery. These were previous myocardial infarction, history of angina, history of hypertension, history of renal failure and history of heart failure. In the conditional logistic regression model derived by stepwise regression, myocardial infarction and renal failure were found to be significant risk factors ($P <$ 0.03), with hypertension at a borderline level of 0.052.

It was found that angina made a significant contribution to the regression model if a history of myocardial infarction was not included in the equation. When a history of myocardial infarction was included in the model the term for angina ceased to be significant. That is to say, most of the risk caused by ischaemic heart disease could be accounted for by the term for myocardial infarction.

Much of the heart failure reported in this population was probably a result of ischaemic heart disease or hypertension. The absence of heart failure in the final regression model may be accounted for by the inclusion of terms for myocardial infarction and hypertension. In the absence of these terms, heart failure made a significant contribution to the model.

Failure to find a perioperative risk associated with diabetes mellitus is difficult to explain. It may be that there was a bias in the recording of the cause of death in diabetics, such that some perioperative cardiovascular deaths of diabetics were coded as being caused by diabetes rather than by a cardiovascular event.

METHOD OF ANALYSIS

A predictive or prognostic equation, such as the one reported here, is useful for identifying patients at risk. However, a distinction should be made between predictive and explanatory models. A predictive equation aims to predict outcome on the basis of the patient's exposure to risk factors, but it does not necessarily give an accurate impression of the importance of individual risk factors. An explanatory equation is intended to give the best possible estimate of the effect of one or more risk factors.[13 14] The distinction can be illustrated using the current data. There is a complex interaction between various cardiovascular risk factors. One risk factor may lie on the causal pathway for the effect of another. For example, hypertension has a role in the pathogenesis of ischaemic heart disease and patients with hypertension are more likely to have suffered myocardial infarction. A history of myocardial infarction may account for some of the perioperative cardiovascular risk associated with hypertension. Our prognostic equation included both hypertension and myocardial infarction. Adjustment for myocardial infarction may reduce the effect of hypertension. Thus the regression coefficient for hypertension may not reflect the full impact of hypertension on risk.

COMPARISON WITH OTHER STUDIES

For the most part, our findings were similar to those of other workers. Many studies, including those of Goldman and colleagues,[6] Larsen and colleagues[5] and Fowkes and colleagues,[7] have identified an association between previous myocardial infarction and perioperative cardiovascular complications. An association between renal impairment and adverse outcome has also been demonstrated in other studies.[9 11]

There are some interesting contrasts with other studies. The effect of a history of hypertension on adverse outcome is not clearly established. Prys-Roberts, Meloche and Foëx demonstrated associations between poorly controlled hypertension, intraoperative cardiovascular instability and myocardial ischaemia.[15] The multicentre study of general anaesthesia conducted in North America found an association between preoperative hypertension and perioperative bradycardia, tachycardia and hypertension.[1] Browner, Li and Mangano identified an association between history of hypertension and mortality after major non-cardiac surgery.[11] In contrast, hypertension was not found to be a significant risk factor on multivariate analysis in the studies of Foster and colleagues,[8] Pedersen, Eliasen and Henriksen,[10] Larsen and colleagues[5] or Goldman and colleagues.[6]

We found heart failure to be a risk factor on univariate analysis, but not after adjusting for other risk factors. Other studies have found heart failure or poor left ventricular function to be a risk factor for adverse outcome on multivariate analysis.[5 8 10]

In trying to understand these differences it must be remembered that the various studies examined different populations in different locations, and that the study designs and methods of data collection varied. Goldman and co-workers, and Larsen and colleagues, studied patients more than 40 yr of age undergoing both elective and emergency non-cardiac surgery.[5,6] Fowkes and colleagues[7] examined outcome after all 108 878 anaesthetics given in Cardiff between 1972 and 1978. Pedersen, Eliasen and Henriksen studied all patients undergoing anaesthesia in one hospital over a 1-yr period, no lower or upper age limit being specified for the inclusion of patients.[9,10] Browner, Li and Mangano studied US veterans aged 38–89 yr undergoing major non-cardiac surgery.[11] Shah and colleagues studied patients who were more than 70 yr of age or known to have cardiac disease.[3] The observations of Forrest and co-workers were made in the context of a multicentre, randomized study of four different anaesthetic agents.[2] Also, the end-point used varied from study to study. We took cardiovascular death as an end-point. In the study by Shah and colleagues, the end-points were identified by review of the medical records and included angina, myocardial infarction, heart failure and cardiac death.[3] Goldman and colleagues[6] used adverse cardiovascular events as identified by the study observers and confirmed on diagnostic testing, while Foster and co-workers[8] used cardiovascular events reported to the CASS registry. Given these differences, the relative consistency of the different studies is encouraging, while the fact that there are some differences both between the studies and between our findings and those of other workers is not surprising. These differences may result in part from random error or in part from real differences between the populations studied.

WEAKNESSES OF THE STUDY

Patients in this study were selected from the Oxford Record Linkage Study on the basis of a cardiovascular cause of death recorded in any of the sections of their death certificate. It is well established that diagnoses recorded on death certificates often do not reflect the true cause of death.[16,17] Using the medical records it was possible to identify patients who had suffered a series of surgical and medical complications before death, and it appeared that a diagnosis of heart failure or cardiac arrest had been seized upon to simplify an otherwise very complex picture. Many of these misdiagnoses could be identified from the medical records and such patients were excluded. It is possible, however, that in some cases a diagnosis of cardiovascular death was mistakenly taken at face value.

The research nurse who examined the medical records could not be blinded to the patient/control status of subjects as outcome was usually clearly recorded in the notes. The question therefore arises of possible observer bias in the recording of data on hypertension. This problem was addressed by the use of a data collection tool which demanded specific responses to a series of questions rather than asking more general questions about the observer's impression of the course of events.

It could be argued that this study was overmatched in the manner described by Rothman.[18] That is, the matching criteria were demanding and it proved impossible to match 25 subjects, so reducing the efficiency of the study. Matching on type of surgery was probably justified in that this is a potential confounder which has many categories and is difficult to quantify more simply. Matching on consultant may also be justified. Matching on age was probably necessary to avoid the possibility of identifying controls who were appreciably younger than the patients. It would have been possible to control for age in the analysis and at the same time gain information on the association between age and adverse outcome. Frequency matching would have been sufficient. The effect of sex could possibly have been controlled in the analysis. Without matching on sex, information could have been gained on the effect of sex on perioperative risk. Finally, matching on date of surgery would have been useful and was attempted, but led to the loss of a large number of pairs through failure to match.

CONCLUSIONS

Our study is consistent with previous work in identifying myocardial infarction and renal failure as risk factors for perioperative cardiovascular complications. Unlike some previous studies, we did not identify heart failure as a risk factor on multivariate analysis. In this study, where data were examined by multivariate analysis, hypertension achieved a significance level of $P = 0.052$ for adverse outcomes. Although univariate analysis of this dataset and that of our previous publication suggested a strong association between hypertension and adverse outcome, such a statistical approach does not take into account other confounding factors.

It may be argued that further work is justified. Cross-sectional studies or further case-control studies would provide a means of studying this problem without the substantial resources needed for a major cohort study. However, it must be remembered that the overall risk of death after anaesthesia and surgery is low.[2] The impact of cardiovascular risk factors is greatest in populations in which the underlying risk is greatest, such as in vascular and other major surgery. It is towards such groups that future investigations should be directed.

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Myocardial ischaemia after coronary artery bypass grafting: early *vs* late extubation

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Summary

The technique of early extubation after coronary artery bypass grafting is increasing in popularity, but its safety and effect on myocardial ischaemia remain to be established. In a randomized, prospective study, patients undergoing routine elective coronary artery bypass grafting were managed with either early or late tracheal extubation. The incidence and severity of electrocardiographic myocardial ischaemia were compared. Data were analysed from 85 patients (43 early extubation; 42 late extubation). Median time to extubation was 110 min in the early extubation patients and 757 min in the late extubation patients. After correction for randomization bias, there were no significant differences between groups in ischaemic burden, maximal ST-segment deviation, incidence of ischaemia and area under the ST deviation–time curve (integral of ST deviation and time). Similarly, there were no differences between groups in postoperative creatine kinase MB-isoenzyme concentrations and duration of stay in the ICU or hospital. Therefore, this study provides evidence for the safety of early extubation after routine coronary artery bypass grafting. (*Br. J. Anaesth.* 1998; **80**: 20–25)

Keywords: heart, ischaemia; heart, coronary artery bypass grafting; intubation tracheal

Traditionally in the anaesthetic management of coronary artery bypass grafting (CABG) attempts are made to attenuate the stress response to surgery, often using high-dose opioids and late tracheal extubation after a prolonged period of postoperative sedation and ventilation. In practice, use of a low-dose opioid balanced anaesthetic technique allows tracheal extubation to be performed within 1 h of surgery.[1] However, recent studies have revealed a high incidence of postoperative myocardial ischaemia within the first 8 h after CABG, which may be associated with adverse cardiac outcome.[2–4] Postoperative high-dose opioid sedation and other measures designed to attenuate the stress response have been shown to reduce postoperative myocardial ischaemia.[5–6] Although demonstrable cost savings and shortened ICU and hospital stays[7–9] have led to the increasing popularity of early extubation, the safety of performing tracheal extubation during this high-risk period for myocardial ischaemia remains to be established. We have therefore carried out a randomized, prospective study using continuous ECG monitoring to compare the occurrence of myocardial ischaemia between an early extubation, low-dose opioid technique and a late extubation, high-dose opioid technique.

Patients and methods

After obtaining approval from the local Ethics Committee and written informed consent, we studied 98 patients undergoing routine elective CABG. We excluded those patients who were unlikely to be suitable for early extubation or who had ECG abnormalities making the diagnosis of myocardial ischaemia difficult. These included patients aged more than 71 yr, those receiving digoxin, and those with left or right bundle branch block on preoperative ECG (QRS duration $\geq$0.12 s), morbid obesity (body mass index greater than 35), FEV_1 or FVC values less than 50% of predicted or poor left ventricular function (CASS score[10] greater than 15 or ejection fraction <30%). Data collected included: age, sex, history of previous myocardial infarction, hypercholesterolaemia, smoking, hypertension, diabetes mellitus, preoperative use of nitrates, calcium antagonists, beta blockers and CASS score obtained at preoperative cardiac catheterization.

PEROPERATIVE MANAGEMENT

Anti-anginal medication was continued up to and including the morning of surgery. Patients received oral diazepam 0.1 mg kg^{-1} as premedication 2 h before surgery. On arrival in the operating room, patients were allocated to either early extubation (group E) or late extubation (group L), according to a prepared randomization schedule. Group E patients received fentanyl 50 μg kg^{-1}; group L patients received fentanyl 15 μg kg^{-1}. Anaesthesia was induced in both groups using either etomidate or diazepam. Neuromuscular block was produced with vecuronium, and anaesthesia was maintained with isoflurane in 100% oxygen. At the end of surgery,

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group E patients were given neostigmine 0.03 mg kg^{-1} and glycopyrrolate 0.06 mg kg^{-1} to antagonize residual neuromuscular block.

Cardiopulmonary bypass was performed using a membrane oxygenator. All operations were performed by one of two surgeons (B. F. and W. I. W.) using either anterograde–retrograde warm blood cardioplegia with systemic normothermia or intermittent cross-clamp/fibrillation with moderate systemic hypothermia (30–32 °C). Surgeons were asked to assess the quality of the grafts and distal run-off as excellent, good, fair or poor, and to assess the overall quality of myocardial revascularization as either satisfactory or unsatisfactory. Total duration of aortic cross-clamping and duration of cardiopulmonary bypass were recorded.

POSTOPERATIVE MANAGEMENT

After transfer to the intensive care unit (ICU), group L patients received i.v. infusion of propofol 50–300 mg h^{-1} without the use of a loading or bolus dose. Sedation with propofol was maintained such that patients were unresponsive to tracheal suction or gentle shaking. If sedation lightened they were given i.v. boluses of morphine 5 mg, and the propofol infusion was increased until sedation reached the required level. After a period of at least 8 h, propofol infusion was discontinued and patients were allowed to awake. Group E patients were allowed to awake immediately after entering the ICU.

Patients in both groups were excluded from the study if they failed to fulfil the following criteria throughout the period of ECG monitoring: haemodynamically stable (not requiring more than 6.5 μg h^{-1} of epinephrine); blood loss less than 120 ml h^{-1} and arterial P_{O_2} $\geqslant$10 kPa with an inspired oxygen concentration of 50%; and PEEP$\leqslant$5 cm H_2O. Tracheal extubation was carried out when the patient was awake and co-operative and could maintain an arterial P_{CO_2} $\leqslant$7 kPa during spontaneous respiration. Patients in group E had a target time to extubation of within 8 h of admission to the ICU. The trachea of patients in group L was extubated more than 8 h after admission to ICU but before the end of the study (24 h after induction of anaesthesia). After extubation, analgesia was provided using i.v. morphine delivered by patient-controlled analgesia devices.

Direct arterial pressure and heart rate were recorded every 5 min in the ICU using Marquette Tramscope 12 monitors archived to a desktop computer.

ELECTROCARDIOGRAPHY

An AM Holter monitor (Series 8500, Marquette Electronics) was attached to the patient at the time of induction of anaesthesia and monitoring was continued for 24 h, except while the patient was on cardiopulmonary bypass. Three ECG leads were recorded (modified CMV4, modified CMV5 and CS-AVF1). Holter tapes were analysed by two investigators blinded to the study group and clinical details, using a Marquette series 8000 automated ECG analysis system and standard techniques. All abnormal QRS complexes including artefact, ventricular ectopics and beats with bundle branch block were excluded. Patients with fewer than 10 h of acceptable beats in the post-bypass period were excluded. Beats classified as normal were subjected to ST-segment analysis. ST-segment deviation from the isoelectric point was trended continuously, both at the J-point and at J + 60 ms. If the J + 60 ms point was on the T-wave, ST deviation was measured at J + 40 ms. Episodes of myocardial ischaemia were defined as: either ST elevation of $\geqslant$2 mm or ST depression of $\geqslant$1 mm, measured as absolute deviation from the isoelectric point. In all analyses ST segment changes had to persist for more than 1 min and had to be reversible for at least 1 min before the end of the recording. For each ischaemic episode a sample of the ECG trace was printed as hard copy and reviewed by two investigators (S. T., P. B.) to exclude artefact. In each patient who had one or more ischaemic episodes the following were calculated: ischaemic burden (total duration in all three leads of ischaemia divided by number of hours monitored); area under the ST-deviation–time curve (AUC), which was also corrected for the number of hours monitored; and average maximal ST-segment deviation during the ischaemic episode. For each ischaemic episode, systolic arterial pressure and heart rate at the time of onset were compared with the median values for the preceding 25 min. A change of $\geqslant$20% was regarded as indicating an episode of ischaemia which was related to haemodynamic alteration. The incidence and characteristics of ischaemia occurring in the pre-bypass period (between induction of anaesthesia and onset of cardiopulmonary bypass) were also recorded.

CARDIAC OUTCOME MEASUREMENTS

The following were recorded for each patient: duration of stay in hospital; concentrations of MB isoenzyme of creatine kinase (CK-MB) on the first 3 days after operation; and daily 12-lead ECG for the first 3 days after operation. Non-fatal myocardial infarction was defined as a concentration of CK-MB greater than 130 iu $litre^{-1}$ and development of a new Q-wave ($\geqslant$40 ms and $\geqslant$0.4 mV) or new left bundle branch block on the postoperative 12-lead ECG. The incidences of in-hospital death, use of intra-aortic balloon pump and ventricular arrhythmias requiring treatment were also recorded.

STATISTICAL METHODS

During the design of the study, a 1-mm difference in maximal ST-segment deviation between the early and late extubated groups was felt to represent clinically important effects of different extubation policy. As such this study was designed to be 80% confident that should such differences be observed, they were attributable to extubation policy and not chance. Estimates based on the variability seen in previous studies[5] indicated that approximately 40 patients in each limb of the study were necessary to achieve this power.

Categorical data are presented as counts and continuous data as median (5th and 95th centiles). All continuous data received a test of normality. The integrity of the randomization was checked by exploring the possibility that differences between patient characteristics, preoperative and operative variables stratified by early or late extubation were attributable to something other than chance using a chi-square or Fisher's exact test for categorical data or a Wilcoxon rank sum test for continuous data. Differences in postoperative ischaemia and other outcome measures were similarly explored. $P \leq 0.05$ was considered significant for these univariate analyses.

Table 1 Reasons for failure to complete study (number of patients)

	Group E (n=50)	Group L (n=48)
Electrical interference	1	2
Left bundle branch block	0	1
Right bundle branch block	0	1
Died	0	2
Poor arterial blood-gas values	1	0
Failed early extubation	3	0
Excess blood loss	2	0
Total	57	54

Table 2 Patient and preoperative clinical data (mean (range) or number)

	Group E (n=43)	Group L (n=42)	P
Age (yr)	58.4 (38–70)	61.1 (44–70)	0.35
Sex (M:F)	35:8	36:3	0.59
Height (cm)	172 (157–180)	167 (157–178)	0.18
Weight (kg)	80 (56–101.5)	79.5 (60–94.5)	0.66
Previous MI	23	25	0.48
Diabetes mellitus	4	5	0 66
Hypertension	17	8	0 03
Smoking	36	34	
Hypercholesterolaemia	10	14	0.30
Medications			
Beta blockers	34	24	0.03
Calcium antagonists	33	32	0.95
Nitrates	31	35	0.21
CASS score	8 (5–14)	7 (5–14)	0.95

Table 3 Surgical data (median (5th and 95th centiles)). *Chi-square result for all grafts

	Group E (n=43)	Group L (n=42)	P
Aortic cross-clamp time (min)	45 (25–77)	43 (26–68)	0.37
Cardiopulmonary bypass time (min)	118 (65–203)	106 (0–152)	0.13
No. of grafts received			
1	0	0	
2	5	5	
3	7	9	
4	24	22	
5	7	6	0.94*
Surgeon's assessment of individual grafts			
Excellent	64	63	
Good	47	54	
Fair	41	32	
Poor	10	6	0.48*
Satisfactory revascularization	38	35	
Unsatisfactory revascularization	5	7	0.50

Table 4 Characteristics of pre-bypass ischaemia (median (5th and 95th centiles))

	Group E (n=43)	Group L (n=42)	P
No. of patients with pre-bypass ischaemia	9	10	0.75
Duration of ischaemia (min)	52 7 (5.2–101.6)	18 (1.5–73)	0.25
Area under the curve (mm min)	23.5 (5.5–124.7)	23.5 (1.4–1330)	0.32
Maximal ST-segment depression (mm)	1.3 (1.2–1.6)	1.4 (0–2 6)	0.14

Results

Of the 98 patients admitted to the study, ECG analysis was completed in 85 patients. Reasons for exclusion of the remaining 13 patients are given in table 1. These 13 patients were excluded from further data analysis.

PREOPERATIVE AND SURGICAL DATA

Although patients were allocated randomly to study groups, analysis of preoperative data (table 2) revealed higher prevalences of essential hypertension ($P = 0.038$) and beta-blocker therapy ($P = 0.030$) in the early group. This prompted the use of multivariate analysis of covariance to assess the true effects of extubation policy on postoperative ischaemia, independent of these confounding factors.

There were no other differences between groups in patient and clinical preoperative data, surgical assessment of graft quality or quality of revascularization (table 3).

TRACHEAL EXTUBATION

Median times to tracheal extubation were 110 (range 4–255) min in group E and 757 (499–1240) min in group L. Of the 13 patients who failed to complete the study (table 1), four patients were excluded because of extubation problems: in three patients in group E the trachea could not be extubated within the designated period of 8 h because of inadequate Pa_{CO_2} or Pa_{O_2} values during spontaneous breathing and one patient in group E had inadequate arterial $P\mathrm{o}_2$ in the period before extubation.

USE OF GLYCERYL TRINITRATE AND EPINEPHRINE

More group E patients (77%) than group L patients (48%) received glyceryl trinitrate in the ICU (P = 0.006); 14% of group E patients *vs* 31% of group L patients received epinephrine in the ICU (P = 0.06).

PRE-BYPASS ISCHAEMIA

Nine patients in group E and 10 in group L had pre-bypass ischaemia. There were no significant differences between groups in the prevalence, duration, AUC or maximal ST-segment deviation of ischaemia in the pre-bypass period (table 4).

POST-BYPASS ST CHANGES

Median duration of monitoring in the postoperative period was 19 (range 14–21) h for group E and 19 (11–21) h for group L

ST depression and ST elevation

Twenty-two of 43 (51%) group E patients and 17 of 42 (40%) group L patients had episodes of ST depression or ST elevation, or both (P = 0.323) in the post-bypass period (fig. 1). When other ST characteristics (AUC, ischaemic burden and maximal ST deviation) were examined, analysing only those patients with ST changes, there were no significant differences between groups (table 5, fig. 2).

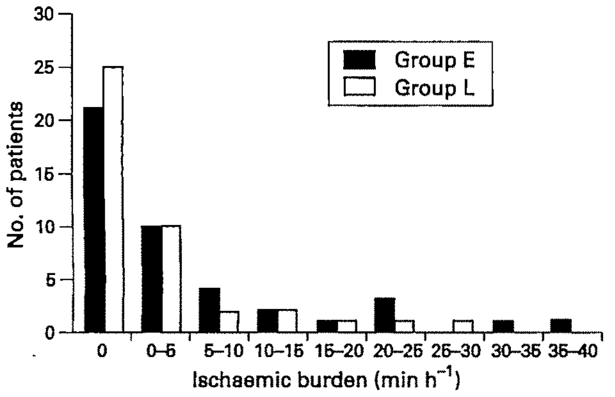

Figure 1 Distribution of ischaemic burden in patients in groups E and L with ischaemia characterized by ST elevation or ST depression.

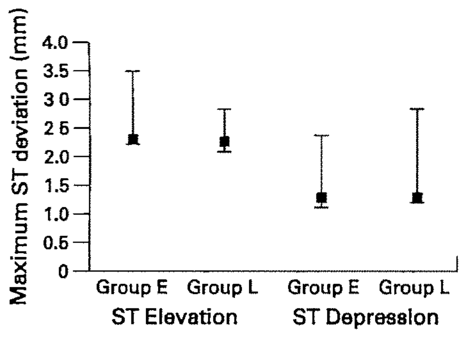

Figure 2 Maximum ST-segment deviation during ischaemic episodes in patients in groups E and L (median (5th–95th centiles)).

ST depression alone

Twenty of 43 (47%) patients in group E compared with 11 of 42 (26%) in group L had episodes characterized by ST depression (P = 0.029, chi-square test).

Analysis of patients with ST depression revealed no differences in other characteristics of ischaemia between early and late extubation patients (table 6). However, when all patients (i.e. those with or without ST changes) were included in analysis of characteristics of ischaemia, there was a greater ischaemic burden and AUC in the early extubation group (mean ischaemic burden in group E = 4.06 mm h^{-1} *vs* group L = 1.98 mm h^{-1}, P = 0.044; mean AUC in group E = 5.28 mm min *vs* group L = 2.75 mm min, P = 0.044). MANOVA analysis was used to correct for the influence of the excess of patients with essential hypertension and preoperative beta-blocker therapy in the early group. This resulted in no significant differences between groups (P = 0.440 for AUC, P = 0.383 for ischaemic burden).

In general, ST segment changes were not related to alterations in heart rate or arterial pressure (six of 204 ischaemic episodes in group E; 10 of 155 episodes in group L were related to haemodynamic changes). Similarly, ST changes did not appear to be related to tracheal extubation: only 15 of 204 ischaemic episodes in group E and four of 155 episodes in group L occurred within 30 min before or after extubation.

OUTCOME MEASUREMENTS

Two patients (group L) died during their hospital stay, both during the postoperative ECG monitoring period while in the ICU, both with acute cardiac failure. Two patients in group E and two in group L developed non-fatal MI (new significant Q-waves or new left bundle branch block, and CK-MB values greater than 130 iu litre^{-1} in any of the first 3 days after operation). Of the four patients who developed non-fatal MI, three had ischaemia in the postoperative period. None of the four patients had pre-bypass ischaemia. Plasma CK-MB values were similar in both groups on postoperative days 1 and 2. No patients developed sustained ventricular arrhythmias, required an intra-aortic balloon pump or died in hospital after discharge from the ICU to the general wards. Time spent in the ICU and duration of hospital stay were similar in the two groups (table 7).

Table 5 Characteristics of post-bypass ischaemic episodes· analysis of patients with ischaemia as defined by both ST elevation and ST depression (median (5th and 95th centiles))

	Group E (n=43)		Group L (n=42)		P
No. of patients with ischaemia	22		17		0.32
Ischaemic episodes					
Ischaemic burden (mm h^{-1})	5.65	(0 19–34.0)	4.5	(0 53–27.1)	0.52
Area under the curve (mm min h^{-1})	10.0	(0.2–38.9)	8.23	(0 56–43 4)	0.68
Max. ST deviation					
ST elevation (mm)	2.31	(2.23–3.5)	2.26	(2.1–2.83)	0 40
ST depression (mm)	1.28	(1.13–2.36)	1.3	(1.2–1.82)	0 36

Discussion

We have measured the duration and severity of pre- and postoperative ischaemia by recording ST-segment depression and elevation. The only significant difference in outcome between the late and early groups was a greater prevalence of ST depression ischaemia in the early group. The validity of this finding must be interpreted in light of a pre-existing potential bias after randomization of patients: an excess of hypertensive patients in the early group. No reason other than chance could be invoked to explain the occurrence of such a randomization bias. Essential hypertension in patients with good left ventricular function is often treated by beta-adrenergic block, the significant difference between the two groups in

Table 6 Characteristics of post-bypass ischaemic episodes· analysis of patients with ischaemia defined by ST depression alone (median (5th and 95th centiles))

	Group E (n=43)		Group L (n=42)		P
No. of patients with ischaemia	20		11		0.02
Ischaemic burden (min h^{-1})	4 5	(0.13–28 7)	6.14	(0.61–27 1)	0.70
Area under the curve (mm min h^{-1})	5.66	(0.13–36.3)	6.71	(0.63–33.1)	·0.70

Table 7 Outcome measurements (median (5th and 95th centiles))

	Group E (n=43)	Group L (n=42)	P
No of patients with non-fatal MI	2	2	0.82
CK-MB day 1 (iu litre^{-1})	56 (29–280)	57 (31–87)	0.58
CK-MB day 2 (iu litre^{-1})	42 (16–185)	40 (15–162)	0.65
Hospital stay (days)	8 (6–12)	8 (7–10)	0 75
ICU stay (days)	2 (2–2)	2 (2–4)	0.55

the use of these drugs is therefore not surprising. When MANOVA was used to correct for this bias, differences in ischaemia between groups disappeared. This raises the possibility that the greater prevalence of ST depression ischaemia was a result solely of the greater prevalence of essential hypertension in group E. This is supported by previous findings of characteristically abnormal diastolic ventricular function in hypertensive patients with abnormal coronary blood flow leading to a greater risk of compromised perfusion and myocardial ischaemia.[11–14]

The use of continuous ECG monitoring to detect myocardial ischaemia is well established. Nevertheless, there is no universally accepted "gold standard" for the detection of myocardial ischaemia in the postoperative situation and it is now appreciated that caution is also necessary in the ECG diagnosis of ischaemia because of the high incidence of ECG abnormalities after CABG compared with non-cardiac surgery.[15] Criteria for interpretation of post-CABG ECG ischaemia are still evolving. In our study we used criteria comparable with those of the SPI group[2 3 5] to define ischaemic episodes. Our separate analysis of ST-segment depression episodes in addition to analysis of combined ST depression and ST elevation allows more direct comparison with other studies which have used ST depression alone as a marker of ischaemia,[16 17] and with studies which have examined both ST elevation and ST depression but found significant results with ST depression alone.[5]

A variety of ECG leads have been used in previous studies. Two of the three leads used in our study (modified CM-V4, CM-V5) should have detected at least 90% of ischaemia compared with full 12-lead electrocardiography,[18] and the use of the third lead CS-AVF1 detects ischaemia occurring in the distribution of the left and right circumflex and left anterior descending coronary arteries,[19 20] and increases sensitivity of ischaemia detection to 96%.[21]

More patients in group E compared with group L received glyceryl trinitrate (GTN) to treat emergence hypertension after operation. More group L patients received epinephrine after operation although this was not significant. These findings were probably a result of the well recognized hypotensive effect of deep sedation and propofol,[22] despite avoidance of an initial loading or bolus dose. A confounding effect of GTN is unlikely, as GTN has been shown to have no effect on myocardial ischaemia during CABG.[23]

In six (12%) of a total of 50 patients originally allocated randomly to group E, the trachea could not be successfully extubated early. This incidence is comparable with previous studies.[24 25] With current anaesthetic and surgical techniques, it seems likely that an irreducible small proportion of patients fail early extubation. This however does not negate the overall validity or usefulness of the technique.

Previous studies have examined post-CABG myocardial ischaemia, and have reported incidences of myocardial ischaemia ranging from 3%[26] to 48%.[3] This wide range reflects differing methods and criteria for diagnosing myocardial ischaemia, in addition to different therapies and patient populations. Nevertheless, the overall incidence of ischaemia in our patients was comparable with that of other studies. Our finding that ischaemic episodes were not related to haemodynamic instability[3 5 20 21] or to tracheal extubation[27] is similar to the findings of other studies.

The SPI group compared deep sufentanil–midazolam sedation with morphine–midazolam for patients who underwent ventilation after CABG and found that the sufentanil group had less severe ST-segment depression than the morphine group.[5] This study was one of the first to raise the issue of post-CABG ischaemia. In both groups in this study the trachea was extubated late. Their sufentanil group received considerably more opioid than the morphine group, and the greater severity of ischaemia in the morphine group may reflect relatively poor analgesia and sedation in patients receiving artificial ventilation via a tracheal tube. In our study, patients were either kept deeply sedated or the trachea was extubated and patients given adequate analgesia with patient-controlled morphine administration. This may account for the similarity between our two study groups.

One other study has directly compared ischaemia in early and late extubation after CABG.[25] In this study, anaesthetic and postoperative management were broadly similar to the present study, although sedation was with midazolam in late extubation patients and propofol in early extubation patients. Although a trend is apparent, with early extubation patients having a higher incidence of ischaemia in 10 of 12 four-hourly periods in which postoperative ischaemia was recorded, a statistically significant difference in ECG ischaemia could not be demonstrated between study groups, which is consistent with our own findings.

The importance of the stress response in post-CABG ischaemia remains unclear, and the optimum timing and approach to attenuating it are similarly not known.[28] For this reason we have not measured any biochemical indicators of the stress response. However, even allowing for an important role for the stress response in postoperative ischaemia, it appears that plasma catecholamine and steroid concentrations are similar with early or late extubation,[25 29] which is consistent with our finding of no difference in ischaemia between early and late extubation groups. The clinical relevance of this and similar studies rests on the assumption that postoperative myocardial ischaemia is a potential predictor of adverse cardiac outcome, and on the ECG diagnosis of myocardial ischaemia in the post-CABG patient. Although some workers have failed to find such a correlation[5 30 31] raising the possibility that perioperative ischaemia after CABG is in fact a benign epiphenomenon, others have suggested a relationship between postoperative myocardial ischaemia after CABG and adverse cardiac events.[2 3 32] Our study, with a low incidence of adverse cardiac outcome (MI or cardiac death) had insufficient power to add to this particular debate.

In conclusion, when corrected for randomization bias, we found no difference in the prevalence of postoperative myocardial ischaemia in patients whose trachea was extubated within 8 h of surgery compared with those in which extubation occurred later. Early extubation appears to be a safe option, although in our practice we have failed to demonstrate any benefit in terms of duration of ICU or hospital stay.

Acknowledgement

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Mast cell tryptase in anaesthetic anaphylactoid reactions

M. M. FISHER AND B. A. BALDO

Summary

Increased concentrations of mast cell tryptase are a highly sensitive indicator of anaphylactic reactions during anaesthesia. We obtained serum specimens from 350 patients after possible anaphylactic reactions during anaesthesia. Serum was collected from patients in our own institution (27), and transported by mail and courier from other hospitals in response to a request in the medical literature (323). Concentrations of mast cell tryptase were measured in 416 specimens. Intradermal testing was performed in 217 patients and radioimmunoassay for drug-specific antibodies with serum in 198 patients. Mast cell tryptase concentrations were increased in 158 patients, equivocal in 10 and not increased in 182. There was a significant difference in the incidence of positive intradermal tests, radioimmunoassay tests and evidence of an IgE-mediated reaction in patients whose mast cell tryptase concentrations were increased. Seven of 143 patients whose mast cell tryptase concentrations were not increased at appropriate sampling times had positive tests for IgE antibodies, and in 33 of 158 patients with increased mast cell tryptase concentrations no IgE antibodies were detected. We conclude that increased mast cell tryptase concentrations are a valuable indicator of an anaphylactic reaction during anaesthesia. Their presence favours an IgE-mediated cause but does not always distinguish between anaphylactoid and anaphylactoid reactions, and patients in whom mast cell tryptase concentrations are not increased still require skin testing. (*Br. J. Anaesth.* 1998; **80**: 26–29)

Keywords: allergy; complications, anaphylaxis; enzymes, tryptase.

Mast cell tryptase (MCT) is an enzyme released from activated mast cells but not basophils[1] and is detectable in serum 1–6 h after anaphylactic reactions.[2 3] It can be used to diagnose anaphylaxis in post-mortem specimens.[4–6] We report the results of MCT measurements in 350 consecutive patients and their correlation with other allergy tests.

Patients and methods

The availability of the assay was notified and specimens were requested in the Australian anaesthetic literature. Anaesthetists were asked to collect three serum specimens between 1 and 8 h after a suspected anaphylactic reaction during anaesthesia. Specimens were transported frozen. In 26 patients with fatal reactions, serum was obtained at post mortem in 14, ante mortem in nine and at both times in three. After data from the first 40 patients were analysed, the timing was altered to a single test between 1 and 6 h after the start of the reaction. Multiple specimens were still assayed if sent.

Control blood specimens were obtained from patients 1 h after cardiopulmonary bypass,[2] haemorrhagic shock[2] and septic shock.[2]

MCT was assayed using a commercial radioimmunoassay (Pharmacia).

MCT was described as increased if concentrations greater than 3 μg litre^{-1} were detected in ante-mortem specimens, and concentrations greater than 5 μg litre^{-1} in postmortem specimens (2448); concentrations less than 2 μg litre^{-1} were regarded as not increased. Intermediate concentrations were described as equivocal.

MCT concentrations that were not increased were considered to have been obtained at appropriate times if ante-mortem sampling occurred between 1 and 6 h after the reaction, and for postmortem specimens, if the patient died between 1 and 6 h after the start of the reaction and the post mortem was performed within 3 days of death.[4–6] All specimens with increased values were deemed to have been obtained at appropriate times, even if no times were recorded.

Intradermal testing was performed with drugs diluted to concentrations determined unlikely to produce reactions as a result of direct histamine release according to methods described previously.[7–9] Radioimmunoassay (RIA) test for specific drugs used methods described previously.[10–16]

Results

Concentrations of MCT were increased in 158 patients, equivocal in 10 patients and not increased in 182 patients (table 1). In those patients whose MCT concentrations were not increased, the sampling time was inappropriate in 21 and not stated in 18. Fourteen of these patients had evidence of IgE antibodies by intradermal testing,[5] RIA,[5] or both.[3] None of the controls had increased MCT concentrations.

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Table 1 Mast cell trytase concentrations, and results of radioimmunoassay (RIA) and intradermal (ID) testing in 350 patients with adverse reactions during anaesthesia

Group	No. of patients	ID positive/ performed	RIA positive/ performed	IgE detected
MCT not increased	182	11/98	9/96	14/154
No time given	18	0/2	0/7	0/8
Time inappropriate	21	5/9	5/15	7/9
Appropriate sample	143	6/87	4/81	7/137
MCT equivocal	10	0/6	0/2	0/6
MCT increased	158	108/113	72/101	125/158

Table 2 Significance of IgE involvement and positive intradermal tests (ID) and drug-specific radioimmunoassay tests (RIA) in patients with increased and normal mast cell tryptase concentrations performed at an appropriate time (chi-square test)

Group	No. of patients	ID positive/ performed	RIA positive/ performed	IgE detected
MCT not increased	143	6/87	4/81	7/137
MCT increased	158	108/113	72/101	125/130
Chi-square		154.1	78.6	217.6
P		<0 00001	<0.00001	<0.00001

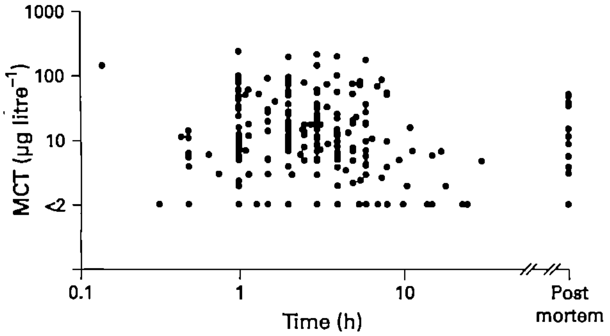

Figure 1 Concentrations of mast cell tryptase (MCT) in patients reacting with suspected anaphylaxis during anaesthesia: 253 measurements in 172 patients with at least one increased value or evidence of immune-mediated reactions, or both.

The results of intradermal and RIA testing in patients with and without increased MCT concentrations are shown in table 2. There was a significant relationship between increased MCT concentrations and positive intradermal tests (chi-square = 74, df = 1, $P = 0.0001$) and between increased MCT concentration and RIA tests (chi-square = 27, df = 1, $P < 0.0001$). On the basis that these tests suggest IgE-mediated reactions, there was a significant association between increased MCT concentrations and immunological IgE-mediated reactions. However, seven patients with evidence of IgE antibodies to a drug and a good clinical history did not show increased MCT concentrations at an appropriate sampling time and in 158 patients with increased MCT concentrations no evidence of IgE antibodies was obtained by intradermal testing in five, RIA in three and both in three. Another 28 patients did not have the appropriate investigations performed to detect IgE antibodies, as intradermal testing was not performed and a valid RIA did not exist.

Figure 1 shows MCT concentrations in patients with at least one increased value or evidence of IgE involvement, or both. The earliest recording of an increased MCT value was at 15 min and the latest at 23 h. However, three patients with increased MCT concentrations between 1 and 6 h showed no increase in specimens obtained before 30 min or after 4 h.

Table 3 Drugs responsible for adverse reactions during anaesthesia in 350 patients. *Patient allergic to thiopental and neuromuscular blocking drugs (NMBD) (ID and RIA positive) given before the reaction

Patients with no evidence of immunological cause (*n*=211)		Patients with IgE detected (*n*=139)	
Drug effect unlikely	30		
Insufficient information	16		
Drug not determined	80		
Drug interaction	2		
Antibiotics	16	Antibiotics	33
Amoxycillin	1	Ampicillin	2
Ampicillin	1	Cefotaxime	1
Cephalexin	1	Cefotetan	4
Cephalothin	6	Cefoxitin	1
Cephalozin	2	Cephalothin	12
Flucloxacillin	2	Cephantemortemandol	1
Gentamicin	2	Cephalozin	5
Vancomycin	1	Flucloxacillin	4
		Penicillin	2
		Vancomycin	1
NMBD	3	NMBD	78
Atracurium	1	Succinylcholine	43
Succinylcholine	1	Atracurium	11
Pancuronium	1	Vecuronium	11
		Alcuronium	8
		Rocuronium	2
		Pancuronium	1
		Mivacurium	1
		Gallamine	1
Colloid solutions	22	Colloid solutions	10
Haemaccel	17	Haemaccel	9
Fresh frozen plasma	2	Normal serum albumin 5%	1
Dextran	1		
Contrast	1		
Normal serum albumin 5%	1		
Other agents	43	Other agents	19
Propofol	15	Thiopental	8
Protantemortemine	9	Thiopental and NMBD*	3
Thiopental	6	Latex	2
Methacrylate	3	Fentanyl	2
Marcain	2	Ondansetron	1
Morphine	2	Pethidine	1
Gortex	1	Fragmin	1
Heparin	1	Morphine	1
Trasylol	1		
Ergometrine	1		

Table 3 shows the drugs responsible for the reactions.

Twenty-six patients died: in 15 the history suggested anaphylaxis, and MCT concentrations were increased in 11, with inappropriate sampling times in three others. In one patient, MCT was increased but the sample was collected in a fluoride tube and control bloods in fluoride tubes showed increased MCT concentrations. In two patients, high concentrations of MCT led to an unsuspected diagnosis of anaphylaxis. In one of these, a coroner's inquest had determined cardiac disease as the cause of death. In nine patients, two ante-mortem and seven postmortem specimens showed no increase in MCT concentrations and RIA tests were negative in seven. None had a history suggestive of anaphylaxis. The RIA test was positive in eight of the 13 patients with increased MCT concentrations and negative in three. In four patients who had post-mortem and ante-mortem specimens, both assays were increased. MCT concentrations in patients who died were significantly higher than the maximum concentrations in patients with IgE-mediated reactions who survived (56.3 (55.5) *vs* 28 (26.8) μg litre^{-1}; $P < 0.05$, Student's *t* test).

Discussion

The classical symptoms of anaphylaxis are more commonly produced in anaesthesia by mechanisms other than true anaphylaxis. Further, the direct histamine releasing effects of anaesthetic drugs may mimic anaphylaxis, and unlike anaphylaxis the clinical features may not recur if the drug is administered more slowly. Thus a test which accurately answered the question "Is this an anaphylactic reaction?" would be of great value. Furthermore, such a test may determine who needed to be investigated by skin or RIA testing subsequently and would be a valuable tool for selecting a homogeneous population to evaluate tests for drug allergy. At present the difficulty in determining who is allergic clinically makes negative tests more difficult to interpret.

Although drug-specific IgE concentrations at the time of reaction may determine the nature of the reaction,[17] such tests are not available for all drugs and are more reliable when positive, with up to 40% false negative results for some drugs.[9] Plasma histamine concentrations may demonstrate an anaphylactoid reaction but these tests are difficult and samples need to be obtained within 10 min of the reaction occurring, a time when resuscitation is a priority. Early studies by Laroche and colleagues[17 18] suggested that demonstration of increased MCT concentrations was associated with immunological reactions, and this was supported by our earlier studies.[5 9]

The results of this study showed that increased MCT concentrations were associated usually with immunological reactions. Unfortunately, this was not invariably so. Four patients who had proven anaphylaxis with a strong history and positive tests (positive RIA tests in two) did not show increases in MCT. It is unlikely that the RIA and intradermal tests were false positives. Laroche and colleagues[18] described a mechanism that may account for this discrepancy involving reactions caused by immunological release of anaphylactic mediators from basophils (which do not release tryptase[1]) and not mast cells. In their series, 50% of such patients had positive skin tests. The potential serious consequences of misdiagnosing anaesthetic anaphylaxis suggests that patients without increased MCT concentrations should be investigated if severe anaphylaxis is likely from the history.

In 33 patients with increased MCT concentrations we found no evidence of an immunological reaction. In 28 of these, intradermal tests were not performed and RIA tests were not available for the likely agent. Five patients had negative intradermal tests and four of these had negative RIA tests. One patient in whom the history was conclusive for allergy to a Gortex vascular graft required high-dose steroids to suppress anaphylaxis and had no histamine responsiveness at the time of testing, but four others had a strong history of anaphylaxis and the intradermal and RIA tests were probably false negatives. It may be that these patients do not have antibodies on skin mast cells. These patients are to be investigated further to endeavour to find the agent responsible.

Although the statistical data showed that increased MCT concentrations were associated with immunological reactions, increased MCT concentrations may occur with direct histamine release. Direct histamine release from mast cells *in vitro* is associated with increased MCT concentrations,[19] and patients with mastocytosis have increased concentrations.[20] A patient in the non-anaesthetic part of this study had repeated uneventful exposures to vancomycin by infusion and died from a bolus dose of vancomycin, with the highest concentrations we have recorded (238 u. litre^{-1}). In this context, reactions to Haemaccel are interesting. Our studies confirmed those of Vervloet and colleagues[21] that 50% of these patients have positive skin tests and yet we have repeatedly been unable to demonstrate anti-gelatin antibodies in patients who react to Haemaccel. The assumption that positive skin tests indicate IgE-mediated reactions may not be valid for Haemaccel, and the tests may demonstrate exaggerated histamine release from skin mast cells.

The cost of performing an MCT test is approximately $A14 per patient. This cost would be justifiable when the tests are negative if the need for intradermal testing (cost $A22–120)[22] is avoided. This also may remove the cost of travel (which often involves long distances in Australia) to the patient. Detection of seven patients with IgE antibodies and no increase in MCT concentrations suggests that patients without increased MCT concentrations still require skin testing.

There were practical difficulties in providing this testing as a laboratory service to anaesthetists: 20% of the request forms did not have the time of sampling which led to the necessity of attempting to acquire this information as it was feared that sending a report of a negative MCT when sampling has occurred at the wrong time may lead to the assumption that anaphylaxis did not occur with adverse consequences for the patient and medico-legal implications for the anaesthetist and laboratory. The tests were performed in batches of 40 tests and five controls, 45 times per year. This has two implications: first, if the result is awaited before follow-up testing, the optimum time for skin testing may be exceeded; second, the results were usually obtained after discharge and filed in the patient's records without being seen by an anaesthetist. Efforts to send a copy of the results to the anaesthetist have been very difficult on many occasions because the test had been ordered by a member of the junior staff.

The data in this study also showed that the suggested time of sampling of 1–6 h[5] should be reduced to 1–4 h as three patients had increased concentrations of MCT within this time but concentrations outside this time were not increased.

The use of the test in fatal reactions confirmed earlier observations[4–6] of unexplained death not caused by anaesthesia, that MCT concentrations obtained in patients who survive between 1 and 4 h after an anaphylactic or unexplained reaction which is fatal may give the diagnosis, with obvious medico-legal implications.

The major causes of the reactions were neuromuscular blocking drugs, antibiotics and Haemaccel, which differ from our previous studies[9] but are in keeping with Australian studies of critical incidents.[23] We believe that this difference is related largely to the emergence of the cephalosporins as a significant cause of anaphylaxis during surgery in the past few years and to the fact that reactions to Haemaccel were not investigated in our previous studies. Of interest is the number of reactions to antibiotics in which MCT concentrations were not increased: Kuenneke and colleagues[24] suggested that non-histamine related cardiovascular abnormalities may be associated with antibiotic administration in 25% of major surgery.

Succinylcholine is now the most common cause of anaesthetic anaphylaxis in Australia as it is in the rest of the world, replacing alcuronium. This is probably related to usage.[9]

The higher number of patients in whom a diagnosis was reached in the group with increased MCT concentrations was related to the higher specificity of the tests in this group but was biased by the more thorough pursuit of results of intradermal testing after an increased MCT was found.

We conclude that MCT is a useful measurement after a possible anaphylactic reaction during anaesthesia. Sampling should occur between 1 and 4 h after a reaction, and the time of sampling and the reaction should be clearly indicated to the laboratory. Increased MCT concentrations are highly suggestive of an immune cause but may reflect direct histamine release. Patients with increased concentrations of MCT must be investigated for an allergic cause and patients without increased MCT concentrations should be investigated if the clinical picture suggests severe anaphylaxis.

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Effect of positive end-expiratory pressure on the incidence of venous air embolism and on the cardiovascular response to the sitting position during neurosurgery

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Summary

We have studied prospectively the effect of 10 cm H_2O of PEEP on the incidence of venous air embolism and on the cardiovascular response to change from the supine to the seated position in a large neurosurgical population. Patients were allocated randomly to receive either PEEP (10 cm H_2O, $n = 45$) or conventional (control, $n = 44$) ventilation. Cardiovascular and respiratory variables were measured in the supine and sitting positions, and monitoring included precordial Doppler probe, pulmonary artery pressure and expiratory carbon dioxide concentration. Venous air embolism was assumed if changes in precordial Doppler sounds occurred, end-tidal carbon dioxide concentration decreased or air could be retrieved from a central venous multi-orifice catheter. The incidence of venous air embolism (26%) did not differ between patients undergoing conventional ventilation and those undergoing ventilation with 10 cm H_2O of PEEP. Venous air embolism was always detected first by alterations in Doppler sounds. Cardiac output was significantly higher in patients undergoing conventional ventilation than in those undergoing ventilation with PEEP in the supine but not in the sitting position. Furthermore, pulmonary vascular resistance increased significantly only in the upright position in those undergoing ventilation with PEEP. The pulmonary artery wedge pressure to central venous pressure gradient did not attain negative values with PEEP or with upright positioning. We conclude that the use of PEEP during neurosurgical procedures performed in the sitting position should be abandoned as it does not decrease the incidence of venous air embolism but is associated with significant adverse cardiovascular effects. (*Br. J. Anaesth.* 1998; **80**: 30–35)

Keywords: embolism, air; position, effects; ventilation, positive end-expiratory pressure; ventilation, mechanical; surgery, neurological

Venous air embolism (VAE) may occur whenever venous pressure at the site of surgery is below atmospheric pressure and it may have devastating effects in patients undergoing neurosurgical procedures in the sitting position. The reported incidence of VAE varies widely, depending on the methods used for its detection, and incidences from 15% to 35% have been reported.[1-3] Positive end-expiratory pressure (PEEP) has been recommended for many years for the prevention and mitigation of the effects of further VAE,[4 5] despite the experimental observation that PEEP may fail to increase intracranial venous pressure.[5] However, PEEP may decrease mean arterial pressure[6] and reverse the left-to-right inter-atrial pressure gradient which might predispose patients with a probe-patent foramen ovale to the risk of paradoxical air embolism.[7] Accordingly, some authors do not advocate routine use of PEEP during craniotomy in the sitting position.[8] Nevertheless, 78% of all hospitals described the use of PEEP in a questionnaire on perioperative management during operations performed in the sitting position.[9]

However, because either only few patients were examined in prospective studies[8 10 11] or data were collected retrospectively,[2 3] differences in patient management and study design may not allow evaluation of the risk:benefit ratio of PEEP during neurosurgical procedures in the sitting position. Therefore, we studied prospectively in a large number of patients the effect of PEEP on the incidence of VAE in seated neurosurgical patients. Haemodynamic variables during ventilation with PEEP in both the supine and sitting positions were also examined, hypothesizing that PEEP (1) decreases the incidence of VAE, and (2) alters the pressure gradient between pulmonary capillary wedge and central venous pressures.

Patients and methods

After obtaining local Ethics Committee approval and written informed consent, we studied prospectively 89 consecutive adult patients (31 men, 57 women; mean age 52.3 (range 18–75) yr) undergoing elective neurosurgical procedures in the sitting position (85 suboccipital craniotomies, four cervical laminectomies) during a 1-yr period. Patients were allocated randomly to either PEEP (10 cm H_2O, $n = 45$) ventilation or conventional ventilation (control, $n = 44$). There were no exclusion criteria.

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All patients were given flunitrazepam 1 mg orally, 1 h before operation. Anaesthesia was induced with propofol 1.5 mg kg^{-1} i.v., alfentanil 50 μg kg^{-1} i.v. and atracurium 0.5 mg kg^{-1} i.v. After tracheal intubation, the lungs were ventilated mechanically with an oxygen–air mixture ($F_{I_{O_2}}$ = 0.5) either conventionally with a PEEP of 3 cm H_2O (control) or a PEEP of 10 cm H_2O. End-tidal carbon dioxide partial pressure was adjusted to 4.0–4.3 kPa. Anaesthesia was maintained by continuous infusion of propofol 5 mg kg^{-1} h^{-1}, alfentanil 125 μg kg^{-1} h^{-1} and atracurium 0.3 mg kg^{-1} h^{-1}. Before application of the skull clamp and before skin incision, a bolus dose of alfentanil 50 μg kg^{-1} was given. Patients in both groups received Ringer's solution 4 ml kg^{-1} h^{-1} and hydroxyethyl starch solution (10% HES 500 ml) during induction. To record arterial pressure, a 20-gauge polyethylene catheter (Viggo-Spectramed, Montigny le Bretonneaux, France) was inserted into the left radial artery. For measurement of pulmonary arterial, central venous and pulmonary capillary wedge pressures, a four-lumen balloon-tipped pulmonary artery catheter (Thermodilution Catheter 7.5 F, Viggo-Spectramed, Montigny le Bretonneux, France) was inserted via the right internal jugular vein. In addition, a multi-orifice (2 side orifices; Arrow, Central Venous Catheterization Set with Blue Flex Tip; Reading, PA, USA) single-lumen central venous catheter allowing air retrieval in case of VAE was inserted via the right internal jugular vein and positioned near the sinus node using an ECG recorded via the catheter.[12] Vascular pressures, ECG and respiratory carbon dioxide partial pressure were displayed on a monitor and recorded continuously on a strip chart recorder.

With the patient in the seated position a precordial ultrasonic Doppler probe (Dual Frequency Doppler, Model 915-AL, Parks Medical Electronics Inc., Aloha, OR, USA) was placed along the right parasternal border. Proper Doppler placement with detection of intravascular air was verified by rapid injection of 5 ml of agitated saline.[13]

After operation, all patients were transferred to the intensive care unit and the lungs ventilated mechanically.

MEASUREMENTS

Heart rate was recorded from the ECG and cardiac output was assessed by thermodilution (Sirecust 961, Siemens, Erlangen, Germany); the average of three measurements was obtained using 10 ml of iced saline. Systemic and pulmonary vascular resistances were calculated from standard formulae. Arterial, pulmonary artery, central venous and pulmonary capillary wedge pressures in addition to airway pressure (air filled system) were measured by electromanometry relative to barometric pressure. Pressures were referenced to the mid-axillary line in the supine position and to the anterior fifth intercostal space in the seated position. All pressure measurements were recorded continuously on a multi-channel strip-chart recorder (Siredoc 220, Siemens, Erlangen, Germany) at a paper speed of 200 mm min^{-1}.

Respiratory variables (respiratory carbon dioxide partial pressure) were measured proximal to the tracheal tube by in-line infrared radiation absorption (Sirecust 961, Siemens, Erlangen, Germany), and tidal volume and ventilatory frequency by a hot wire anemometer (Anemone, Dräger, Lübeck, Germany). Arterial oxygen saturation was measured by pulse oximetry (PM 8050, Dräger, Lübeck, Germany).

For measurement of blood-gas tensions and pH, and concentrations of electrolytes and haemoglobin, arterial blood was obtained from the radial artery and pulmonary artery and analysed with electrodes at 37 °C (Ciba Corning 288 Blood Gas System, Ciba Corning, Fernwald, Germany).

EXPERIMENTAL DESIGN

Patients were allocated randomly to either ventilation with PEEP or conventional ventilation. Cardiovascular and respiratory variables were measured 15 min after induction of anaesthesia in the supine position (baseline) and 15 min after patients had been positioned in the sitting position. There was no surgical stimulation during these measurements. In patients with VAE, simultaneous measurements of central venous and pulmonary artery pressures were obtained and compared with values of these variables during the 15-min period immediately before air embolism in each patient.

During operation, the presence of VAE was assumed if either (1) changes in precordial Doppler sounds occurred,[11] (2) end-tidal carbon dioxide partial pressure decreased suddenly by more than 0.3 kPa in a step manner[14] or (3) air could be retrieved via the central venous catheter. Furthermore, during VAE, changes in mean arterial, pulmonary arterial and central venous pressures, and changes in arterial oxygen saturation (detected by pulse oximetry) were recorded.

STATISTICAL ANALYSIS

Results are reported as mean (SEM) unless otherwise indicated. Haemodynamic data were analysed by two-way analysis of variance for repeated measurements followed by *post hoc* Newman–Keuls test. A chi-square test was used to compare incidences of events between groups during different study conditions. The following *a priori* null hypotheses were tested: ventilation with PEEP (1) does not change the incidence of VAE and (2) does not alter values of cardiovascular variables. Results were considered to be statistically significant with an α error of $P < 0.05$.

Results

INCIDENCE OF VENOUS AIR EMBOLISM

VAE was detected by a Doppler signal suggestive of air entry in 23 patients (26%), 11 undergoing PEEP ventilation and 12 undergoing conventional ventilation. The incidence of VAE did not differ significantly ($P = 0.95$) between patients undergoing PEEP ventilation (24%) and those undergoing conventional ventilation (27%). Aspiration of air in those patients showing signs of air embolism was possible (recovered air volume 4–25 ml) in six patients (55%) in the PEEP group and in five (42%) in the conventional ventilation group. There was no significant

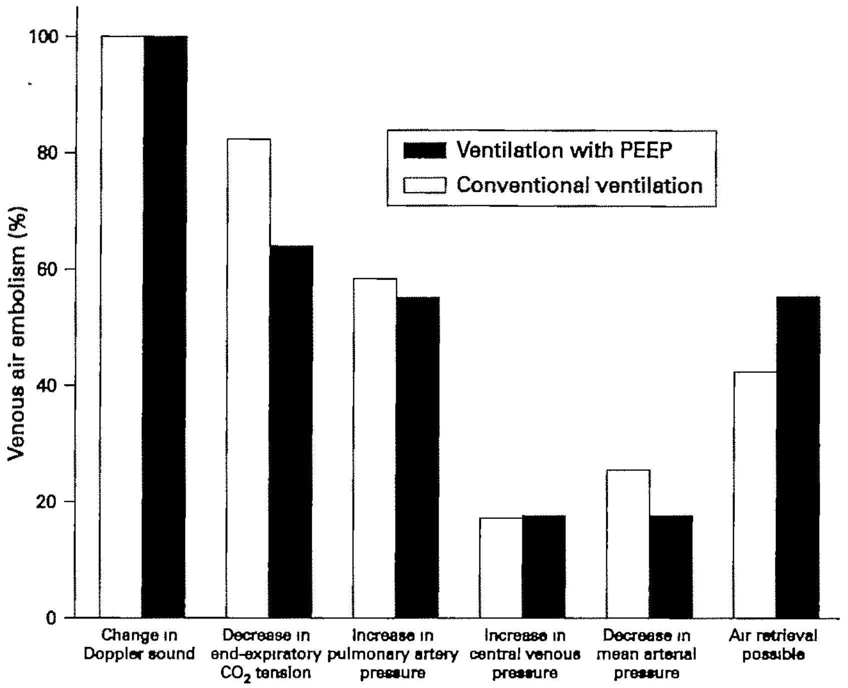

Figure 1 Ability of different monitoring devices to detect venous air embolism in comparison with Doppler in 11 patients undergoing ventilation with 10 cm H_2O of PEEP and in 12 patients undergoing conventional ventilation, demonstrating signs of venous air embolism during neurosurgical operations in the seated position.

difference in the amount of air aspirated or the incidence of successful air aspiration between groups.

INCIDENCE AND SEVERITY OF HAEMODYNAMIC ALTERATIONS AND CHANGES IN END-EXPIRATORY CARBON DIOXIDE TENSION WITH VENOUS AIR EMBOLISM

Approximately 60% of all detected venous air entries were followed by haemodynamic alterations. Most frequently, an increase in pulmonary artery pressure ($n = 13$; 57%) was observed (PEEP group, six (55%) patients; control group, seven (58%) patients), whereas a decrease in mean arterial pressure (PEEP group, two (18%) patients; control group, three (25%) patients) or an increase in central venous pressure (PEEP group, two (18%) patients; control group, two (17%) patients) was seen less often.

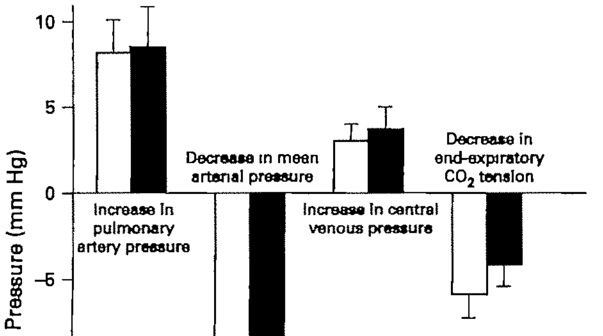

Figure 2 Cardiovascular alterations and changes in end-expiratory carbon dioxide tension associated with venous air embolism in neurosurgical patients undergoing ventilation with 10 cm H_2O of PEEP and in patients undergoing conventional ventilation.

VAE was accompanied by a similar incidence of a decrease in end-expiratory carbon dioxide tension (in seven (64%) patients in the PEEP group and in 10 (83%) patients in the control group). In fact, the mode of ventilation did not alter the sensitivity of different monitoring modalities to detect VAE with alterations in Doppler sounds considered the gold standard (fig.1).

Neither the significant increase in pulmonary artery pressure (PEEP +8.5 (2.4) mm Hg; control +8.2 (1.9) mm Hg) nor the significant decrease in mean arterial pressure (PEEP −14.1 (1.9) mm Hg; control −15.3 (2.1) mm Hg), central venous pressure (PEEP +3.5 (1.4) mm Hg; control +3.0 (0.9) mm Hg) or carbon dioxide tension (PEEP −0.6 (0.2) kPa; control −0.8 (0.2) kPa) associated with air embolism were significantly affected by the amount of end-expiratory airway pressure. Therefore, there was no significant difference in the incidence or severity of cardiorespiratory alterations after VAE between patients in the PEEP and those in the conventional ventilation group (fig. 2).

EFFECT OF PEEP AND POSITIONING ON CARDIOVASCULAR VARIABLES

Moderately but significantly higher pulmonary artery pressure and pulmonary capillary wedge pressure values were observed in the PEEP group compared with the conventional ventilation group both in the recumbent and in the seated position. Central venous pressures was greater with PEEP in the sitting position but not in the supine position. Of note, pulmonary artery wedge pressure was higher than central venous pressures in the supine position in all patients.

When patients were placed in the seated position, pulmonary artery pressure, pulmonary capillary wedge pressure and central venous pressure decreased significantly (table 1). As pulmonary

Table 1 Haemodynamic variables in 89 neurosurgical patients who underwent conventional ventilation (Control) (n=44) or ventilation with positive end-expiratory pressure (PEEP) (n=45), in the supine or sitting position (mean (SEM)). *$P<0.05$ *vs* supine position at baseline; †$P<0.05$ *vs* conventional ventilation

	Supine	Seated
Mean pulmonary artery pressure (mm Hg)		
PEEP	23.7 (0.7)†	19.8 (0.7)*†
Control	21.2 (0.7)	16.1 (0.5)*
Pulmonary artery wedge pressure (mm Hg)		
PEEP	16.8 (0.5)†	13.0 (1.2)*†
Control	14.7 (0.5)	9.3 (0.3)*
Central venous pressure (mm Hg)		
PEEP	14.8 (0.1)	11.2 (0.1)*†
Control	12.9 (0.7)	8.3 (0.4)*
Pulmonary artery wedge pressure to central venous pressure gradient (mm Hg)		
PEEP	2.5 (0.3)	2.1 (0.3)
Control	2.7 (0.3)	1.9 (0.3)
Cardiac index (litre min^{-1} m^{-2})		
PEEP	2.3 (0.1)†	2.1 (0.1)*
Control	2.7 (0.1)	2.3 (0.1)*
Pulmonary vascular resistance index (dyn s^{-1} cm^{-5} m^{-2})		
PEEP	222 (15)	318 (20)*†
Control	226 (22)	240 (16)
Systemic vascular resistance index (dyn s^{-1} cm^{-5} m^{-2})		
PEEP	2740 (125)	3167 (159)
Control	2552 (115)	2845 (106)
Mean arterial pressure (mm Hg)		
PEEP	91.6 (3.0)	86.9 (2.4)
Control	93.1 (2.8)	88.4 (2.2)
Heart rate (beat min^{-1})		
PEEP	57 (1)	56 (1)
Control	59 (2)	60 (2)

capillary wedge pressure remained higher than central venous pressure in all patients, the pulmonary artery wedge pressure to central venous pressure gradient did not attain negative values and did not change significantly with positioning in patients undergoing ventilation with PEEP (P = 0.116) and in those undergoing conventional ventilation (P = 0.233). Figure 3 depicts the pulmonary capillary wedge pressure to central venous pressure pressure gradients of all patients in the PEEP and conventional groups, both in the supine and sitting positions.

As expected, cardiac index was significantly lower in supine patients undergoing ventilation with PEEP compared with those undergoing conventional ventilation; in seated patients, cardiac index decreased markedly in both groups. However, with patients in the sitting position significant differences in cardiac index were no longer observed between groups (table 1).

There was no significant difference between groups in pulmonary vascular resistance while in the supine position. Furthermore, pulmonary vascular resistance increased significantly with PEEP only in the upright position (table 1). Although mean arterial pressure tended to decrease and systemic vascular resistance to increase after attaining the seated position, these differences were not significant with regard to mode of ventilation or body position (table 1).

Discussion

This study was the first to assess prospectively and in a randomized manner the impact of PEEP on the incidence of VAE and on cardiovascular alterations in a large number of patients operated on in the sitting position. We found that ventilation with a PEEP of 10 cm H_2O during neurosurgical procedures in the seated position offered no benefit but rather may be harmful.

Because reliable measurements and interpretation of results depend on central venous and pulmonary artery wedge pressures measured accurately in the supine and seated positions, we referenced all pressures to the mid-axillary line in the supine position and to the anterior fifth intercostal space when patients were in the seated position.[10] [11] There is consensus that pulmonary artery wedge pressure reasonably reflects mean left atrial pressure in the absence of cardiac valve abnormalities and during some unphysiological states (i.e. PEEP values up to 10 cm H_2O or more[15–17]). As the pressure gradient between central venous pressure and pulmonary capillary wedge pressure is normally small, minor differences in the technique of measurement could alter the results obtained. Thus all variables were recorded continuously with each transducer referenced to zero repeatedly and compared between groups at similar times. Another possible source of error is that the pulmonary artery catheter tip might be wedged in regions where pulmonary capillary wedge pressure reflects airway pressure rather than left atrial pressure. However, Benumof and colleagues found important peripheral catheter locations in only 6.9% of patients in whom a pulmonary artery catheter had been inserted.[18] Therefore, from a statistical point of

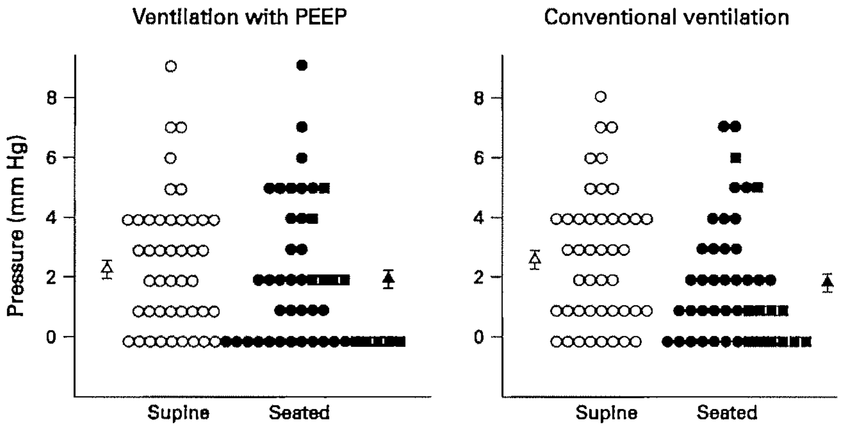

Figure 3 Pulmonary capillary wedge pressure to central venous pressure gradient in 45 patients undergoing ventilation with 10 cm H_2O of PEEP (left) and in 44 undergoing conventional ventilation (right) in the supine and sitting positions. Individual and mean (SEM) values are given. Square symbols indicate patients suffering from venous air embolism.

view, false measurements caused by catheter misplacement are unlikely to have influenced the results in our 89 patients. Furthermore, to avoid possible changes in pulmonary catheter position (e.g. by use of PEEP itself), we ventilated the lungs of our patients with either PEEP or conventionally without changing airway pressure within a study group. Thus pressures measured and comparison between groups should have yielded reliable data.

The overall incidence of VAE (26%) observed in this study is consistent with that reported in several other series.[2 3 11] With no difference in the incidence of VAE with and without PEEP, however, our data do not confirm the results of Lee, Lichtman and Weintraub[19] who reported a decrease in VAE from 55% in patients whose lungs were ventilated without PEEP (n = 9) to 26% in patients who underwent ventilation with 10 cm H_2O of PEEP (n = 19). However, as a PEEP value of up to 15 cm H_2O has no detectable effect on sagittal[20] or transverse[21] sinus pressure in humans, our results demonstrating PEEP to be ineffective in preventing VAE were not unexpected.

We used a precordial Doppler probe to detect VAE. With 0.25 ml of air injected i.v. already altering Doppler sounds,[22] precordial Doppler monitoring is more sensitive in detecting VAE than measurements of end-expiratory carbon dioxide partial pressure or pulmonary artery pressure.[14] However, these latter two methods have the advantage of providing quantitative physiological information on the sequelae of venous air emboli and return of pulmonary artery pressure towards baseline can serve as a guide for the effectiveness of therapy.[23] Our data are in accordance with these reports as changes in Doppler sounds always preceded a decrease in end-expiratory carbon dioxide tension and cardiovascular changes in both the conventional ventilation and PEEP groups. In addition, we could not demonstrate a significant impact of PEEP on the cardiovascular responses associated with VAE.

Historically, the incidence of VAE was associated with procedures on the head, neck, chest and in the post-partum period. Recently, VAE has been detected, for example in orthopaedic hip replacement and abdominal procedures, in addition to neurosurgical procedures in the prone, lateral or supine position.[24] Therefore, VAE is not restricted to the sitting position and it may be speculated if our findings can be applied to these situations.

Pulmonary artery pressure, pulmonary artery wedge pressure and central venous pressure were higher during PEEP ventilation. This is not surprising as PEEP exerts its major cardiovascular effects by increasing intrathoracic pressure.[25] When patients were moved from the supine to the sitting position, vascular pressures decreased regardless of whether or not PEEP was applied, mirroring the decrease in venous blood return to the heart and diminished filling of the pulmonary circulation. These data are consistent with previous results[26 27] demonstrating in spontaneously breathing supine humans assuming the sitting position that intrathoracic blood volume decreased by approximately 300–500 ml with a decrease in both pulmonary artery wedge and central venous pressures. Techniques which are used to maintain filling pressures in the sitting position such as anti-gravity suits or high volume management were not used in this study. However, filling pressures measured in our patients did not differ from those reported in studies using anti-gravity suits.[28 29] As the increase in filling pressures induced by anti-gravity suits has been reported to be only transient in adults[28 30] we rarely use anti-gravity suits in our department. Whether PEEP may be effective in decreasing the incidence of VAE in patients with filling pressures higher than reported so far is beyond the scope of this investigation.

Depletion of the central circulation was also the likely reason for the decrease in cardiac output observed in both groups after patients were seated. However, in the seated position cardiac output in patients who underwent conventional ventilation was not significantly different compared with that during ventilation with PEEP. Presumably, this reflects the pronounced effect of positioning compared with PEEP ventilation or, conversely, the small additional circulatory depressant effect of PEEP in the seated position. Possibly, a much greater increase in PEEP may change this pattern but this has not been evaluated.

While PEEP increased both pulmonary artery wedge pressure and central venous pressure, it failed to affect the pulmonary capillary wedge pressure: central venous pressure gradient. In contrast, Perkins and Bedford reported that 10 cm H_2O of PEEP caused reversal of this pressure gradient in the seated position.[8] However, their results were from only 11 patients, with seven (64%) apparently showing a higher central venous than pulmonary artery wedge pressure during application of PEEP. In contrast, Zasslow and colleagues[10] observed a higher central venous than pulmonary artery wedge pressure in only one of 12 patients whose lungs were ventilated with 20 cm H_2O of PEEP in the seated position. Therefore, with only 11, 12 or six patients per study group, the results of these studies are inconsistent[10 11 31] and may have led to misrepresentation of the risk of developing a negative pulmonary capillary wedge pressure:central venous pressure gradient.

Pulmonary vascular resistance increased significantly only in seated patients in the PEEP group but was not affected by PEEP application in the supine position or by positioning in those ventilated conventionally. Similar to the unchanged pulmonary vascular resistance observed in our conventional ventilation group when seated, pulmonary vascular resistance did not increase significantly in anaesthetized humans whose lungs were ventilated without PEEP when placed in the upright position.[10 27] Most likely, pulmonary vascular resistance increased in our seated patients who underwent ventilation with 10 cm H_2O of PEEP because of the additional impairment of pulmonary vascular filling by positioning, possibly causing smaller pulmonary vascular dimensions and hence increased flow resistance.[32]

The data of this prospective, randomized study in a large number of patients demonstrated that ventilation with 10 cm H_2O of PEEP failed to decrease the incidence of VAE and did not alter the sensitivity of monitoring devices to detect VAE. Furthermore, both PEEP and seated positioning impaired cardiovascular performance, with a small cardiac output measured in seated patients whose lungs were ventilated with PEEP. However, positioning *per se* appears to have had a much greater effect on cardiac output and pulmonary vascular resistance than PEEP. We suggest therefore that routine use of 10 cm H_2O of PEEP during neurosurgery in the seated position has no apparent benefit and cannot be recommended.

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Role of thromboxane and leukotriene B_4 in patients with acute respiratory distress syndrome after oesophagectomy

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Summary

We have studied prospectively the clinical course and serum concentrations of thromboxane B_2 (TxB_2) and leukotriene B_4 (LTB_4) in patients developing adult respiratory distress syndrome (ARDS) after oesophagectomy. The clinical course was assessed according to a validated ARDS score, and intra- and postoperative measurements of TxB_2 and LTB_4 in pre- and post-pulmonary blood were performed in 18 patients undergoing oesophagectomy for oesophageal carcinoma and 11 control patients undergoing thoracotomy and pulmonary resection. Six of 18 patients undergoing oesophagectomy, but no control patient, developed ARDS. The ARDS score was highest on day 8 after operation. Only patients with ARDS had a significant postoperative increase in post-pulmonary, but not pre-pulmonary, TxB_2 concentrations ($P < 0.05$ *vs* patients without ARDS). This study provides evidence that TxA_2, originating from the lungs, was associated with the development of ARDS after oesophageal resection. In view of the high incidence of ARDS after oesophagectomy (10–30%), prophylactic treatment of patients undergoing oesophageal resection with clinically applicable thromboxane synthetase inhibitors may be warranted. (*Br. J. Anaesth.* 1998; **80**: 36–40)

Keywords: lung, adult respiratory distress syndrome; complications, adult respiratory distress syndrome; surgery, gastrointestinal; hormones, thromboxane; hormones, leukotrienes

Adult respiratory distress syndrome (ARDS) is one of the primary contributors to mortality in ICU patients.[1] A wide variety of clinical conditions such as sepsis, burns, trauma[2-4] and major surgery, and oesophageal resections in particular,[5 6] predispose to the development of ARDS. In a meta-analysis of more than 60 000 patients undergoing oesophagectomy, 27% developed ARDS after transthoracic resection and 13% after transhiatal resection.[7] The following factors appear to increase the risk of postoperative ARDS in patients with oesophageal carcinoma: smoking and chronic obstructive pulmonary disease (COPD), transthoracic mobilization of the oesophagus with contusion of the lung during extensive surgery and postoperative (silent) aspiration.[8]

Because of the heterogenity of sepsis or trauma patients, it is difficult to acquire comparable study populations for clinical studies of ARDS. In these patients, the triggering insult for ARDS is seldom predictable and it varies greatly in intensity; also, patient conditions such as age, immune and nutritional status and coexisting medical conditions vary widely. Patients undergoing oesophageal resection for oesophageal carcinoma, however, are a homogenous group, with 1–3 of 10 patients developing ARDS.[7] They are usually aged 50–70 yr, the majority have a history of smoking and preoperative weight loss, they are suffering from the same underlying disease, and the duration and magnitude of the insult triggering ARDS (i.e. oesophageal resection) is uniform. In addition, these patients are unique in that they are exposed to a planned triggering factor (i.e. oesophageal resection) which makes post-oesophagectomy ARDS ideal for prophylactic intervention.

In this study we describe the time course of post-oesophagectomy ARDS as being clinically uniform, with a peak of pulmonary infiltrates on day 7 after operation and a typical distribution pattern of pulmonary infiltrates over the four quadrants. We also measured mediators likely to be involved in post-oesophagectomy lung injury: thromboxane B_2 (TxB_2) and leukotriene B_4 (LTB_4) in arterial and central venous blood of patients undergoing oesophageal resection. Patients undergoing thoracotomy and pulmonary resection served as controls. TxB_2 and LTB_4 were chosen because both mediators have been found to induce acute lung injury in animals and both are increased in patients at risk of developing post-traumatic or septic ARDS.[9 10] In addition, inhibitors of TxA_2 and LTB_4 synthesis are available for clinical use,[1 11 12] and these would allow prophylactic treatment of patients undergoing oesophagectomy.

Patients and methods

After obtaining approval from the regional Ethics

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Committee and informed consent, we studied prospectively 18 consecutive patients undergoing oesophagectomy for oesophageal malignancies and 11 patients undergoing lung resections for pulmonary malignancies (six pneumonectomy, five lobectomy). All patients had combined extradural and general anaesthesia. An extradural catheter was inserted at the T5–7 interspace in all patients before induction of general anaesthesia. An extradural solution containing bupivacaine 1 mg ml^{-1}, fentanyl 2 μg ml^{-1} and epinephrine 2 μg ml^{-1} was infused at a rate of 5–10 ml h^{-1} during operation and maintained for 3–5 days after operation at a rate of 5–15 ml h^{-1}. General anaesthesia was induced according to the departmental routine with thiopental 4 mg kg^{-1}, fentanyl 4 μg kg^{-1} and pancuronium 0.1 mg kg^{-1}, and maintained with 0.3–1.0% isoflurane and 0–70% nitrous oxide in oxygen (according to arterial blood oxygen saturation (Sp_{O_2}>90%)), and repeated intermittent bolus doses of fentanyl and pancuronium as needed. Arterial pressure was monitored continuously via a radial arterial cannula and maintained at a mean arterial pressure of 60–90 mm Hg by adjusting the depth of anaesthesia and infusing blood products, colloids and crystalloids as required. Rarely were catecholamines necessary. The lungs were ventilated to a Pa_{CO_2} of 4.8–5.3 kPa via a left-sided double-lumen tracheal tube, the position of which was controlled by fibreoptic bronchoscopy before surgery started. Arterial oxygen saturation was measured continuously by pulse oximetry and intermittently by arterial blood-gas analysis.

Patients with oesophageal carcinoma were stratified for a one-stage transhiatal or right-sided thoracoabdominal oesophageal resection, according to tumour localization and tumour stage. In all patients undergoing oesophageal resection, the oesophagus was substituted by a gastric tube as described previously.[13 14] A nasogastric tube was placed in the gastric tube for at least 5 days in an attempt to reduce the risk of silent aspiration.[8] After operation all patients undergoing oesophagectomy were kept sedated with morphine 1–7 mg h^{-1} and midazolam 1–5 mg h^{-1}, and their lungs ventilated mechanically via a single-lumen tracheal tube for 48 h and the trachea extubated thereafter, unless they developed pulmonary failure. In the additional 11 patients undergoing right-sided thoracotomy and lung resection (six pneumonectomy and five lobectomy) as a result of bronchial carcinoma, the trachea was extubated at the end of surgery.

All 29 patients were monitored prospectively for development of ARDS. The definition of ARDS used in this study followed the guidelines of the American European Consensus Conference on ARDS: acute onset of bilateral infiltrates seen on chest radiographs with the lowest $Pa_{CO_2}/FI_{O_2} \leq 26.7$ kPa.[15] ARDS severity was assessed using the lung injury score as described by Murray and colleagues[16] (table 1). Lung compliance, positive end-expiratory pressure (PEEP) and Pa_{CO_2}/FI_{O_2} ratio were calculated daily; plain a–p chest x-rays were obtained daily during the early phase of ARDS and every other day in the later course of the illness. Chest x-rays were evaluated by two independent investigators for diffuse infiltrates over the upper and lower pulmonary quadrants.

Table 1 Lung injury score according to Murray and colleagues[16]

	Score
1 X-ray score	
No alveolar consolidation	0
Alveolar consolidation in	
1 quadrant	1
2 quadrants	2
3 quadrants	3
4 quadrants	4
2. Oxygenation score, Pa_{CO_2}/FI_{O_2}	
≥300	0
225–299	1
175–224	2
100–174	3
<100	4
3 PEEP score	
≤5 cm H_2O	0
6–8 cm H_2O	1
9–11 cm H_2O	2
12–14 cm H_2O	3
≥15 cm H_2O	4
4. Total thoracic compliance	
≥80 ml cm H_2O^{-1}	0
60–79 ml cm H_2O^{-1}	1
40–59 ml cm H_2O^{-1}	2
20–39 ml cm H_2O^{-1}	3
≤19 ml cm H_2O^{-1}	4
No lung injury	0
Mild-to-moderate lung injury	0 1–2 5
Severe lung injury	>2.5

Blood samples were obtained simultaneously from a central venous catheter placed in the right atrium and from a radial arterial cannula before surgery, before thoracotomy or during transhiatal dissection of the oesophagus, after closure of the thoracotomy, at the end of surgery and daily after operation between 08:00 and 09:00. Blood was withdrawn into EDTA tubes with indomethacin (to inhibit further leukotriene formation) and centrifuged immediately at 4 °C. Serum was frozen at −80 °C until further processing. At corresponding times, central venous and arterial blood samples were obtained also from patients undergoing lung resection.

ANALYSIS OF EICOSANOIDS

After a SEP-PAK C18-column (Waters, Zürich, Switzerland) extraction from serum, TxB_2, the stable metabolite of the active compound TxA_2, and LTB_4 were measured by commercially available ELISA (Cascade Biochemicals, Reading, UK), as described previously.[17] Intra-assay variabilities for TxB_2 and LTB_4 were 7.8% and 8.4%, respectively; inter-assay variabilities were 8.6% and 6.5%. Normal values in our laboratory for TxB_2 and LTB_4 in venous blood are 115 ± 49 and 89 ± 41 pg ml^{-1} (n = 6). Cross-reactivity for major metabolites for the TxB_2 assay was <1% for PGD_2, 11-dehydro-TxB_2, $PGF_{2\alpha}$ and PGE_2. For the LTB_4 assay, cross-reactivity was 58.8% for LTB_5, 6% for 5(S)-12(S) DIHETE, 4% for 6-trans-LTB_4 and <1% for 5(S)HETE, LTC_4, LTD_4 LTE_4 and prostaglandin metabolites.

STATISTICAL ANALYSIS

Results are presented as mean (SD) for serum concentrations of eicosanoids, mean (95% confidence interval) for the ARDS score and as Σ (sum) of the x-ray score calculated from the six ARDS patients. Regression curves and confidence intervals were calculated using a SigmaPlot software for Windows on a personal microcomputer. Two-tailed Student's t test

Table 2 Patient, preoperative risk and operative data for 18 patients undergoing oesophagectomy (mean (SD) or number). *P<0.05, **P=0.001. VC=vital capacity, TH=transhiatal, TA=thoracoabdominal, HLOS=hospital length of stay

	ARDS	No ARDS
n	12	6
Sex (M/F)	10/2	3/3
Age	62.6 (48–68)	54.3 (42–82)
ASA classification (median (range))	III (II–III)	III (II–III)
Preoperative weight loss (kg)	3 (4 4)	7 5 (1 8)*
Tumour stage		
I	1	0
IIa	3	1
IIb	2	1
III	5	4
IV	1	0
Preoperative VC	3900 (640)	3630 (480)
Preoperative FEV$_1$	2700 (600)	2600 (330)
Preoperative Pa_{O_2}	71.8 (9.1)	71.5 (8.0)
Preoperative Pa_{CO_2}	36 1 (1 1)	34.5 (2.0)
OP (TH/TA)	7/5	2/4
Blood loss (ml)	1280 (550)	830 (470)
Substitution		
Blood (250 ml units)	7.2 (8)	3 (1)
Colloids (ml)	3950 (2100)	3600 (940)
Crystalloids (ml)	8850 (3420)	6020 (1700)
Mechanical ventilation (days)	2.0	14.4 (7.2)
HLOS (days)	26.7 (10)	47.8 (11.8)**

and ANOVA with Bonferroni correction were used to calculate differences between groups. Outcome differences were compared by Fisher's exact test.

Results

None of the patients who underwent pneumonectomy (mean age 68.6 (range 52–76) yr, five males, one female) or lobectomy (mean age 64.5 (range 56–69) yr, five males) developed ARDS. Six of the 18 patients who underwent oesophagectomy developed ARDS during the first 3–5 days after operation, requiring prolonged intensive care therapy, including mechanical ventilation (mean 14.4 (7.2) days). In the other 12 patients the trachea was extubated after 48 h and the patient usually discharged to the ward or to a high dependency unit on the same day. Preoperative weight loss in the ARDS patients was significantly greater than in patients who did not develop ARDS (P < 0.05). All other characteristics and preoperative risk factors were comparable (table 2).

The ARDS score over time in the six ARDS patients is shown in figure 1 (regression with 95% confidence interval (CI)). The highest ARDS score (mean 1.75, 95% CI 1.59–1.91, indicating moderate lung injury)[16] was recorded on day 8 after operation. Pulmonary infiltrates were most prominent in the left lower quadrant (maximum x-ray score of 5 on day 7), followed by the right lower quadrant (maximum x-ray score of 4 on day 8), the right upper quadrant (maximum x-ray score of 3 on day 8) and the left upper quadrant (maximum x-ray score of 1 on day 6) (fig. 2). There was no difference in central venous (i.e. pre-pulmonary) TxB$_2$ concentrations between patients who subsequently developed ARDS and patients who did not develop ARDS. Patients undergoing lobectomy but not pneumonectomy showed a slight (P = 0.09) increase in central venous TxB$_2$ concentrations after closure of the thoracotomy. Only patients developing ARDS had a significant increase in arterial (i.e. post-pulmonary) TxB$_2$ concentrations compared with patients who did not develop ARDS (fig. 3). There was no significant difference in venous or arterial LTB$_4$ concentrations between the different groups, but arterial concentrations tended to be higher than venous concentrations (fig. 4).

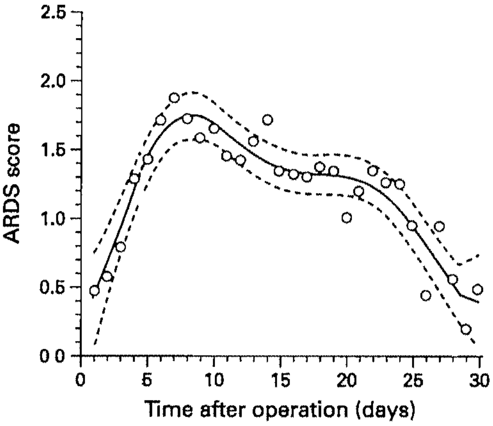

Figure 1 Daily ARDS score for six patients who developed ARDS after oesophageal resection (calculated according to Murray and colleagues[16]). The different points represent the average ARDS score on the given day. Broken lines = 95% confidence interval around the regression curve.

Discussion

The adult respiratory distress syndrome is a severe complication with considerable morbidity and mortality. It occurs frequently after oesophageal resection[7] and requires prolonged intensive care treatment in patients with nutritional and respiratory compromise. Modern multimodal treatment strategies for oesophageal carcinoma, which include preoperative radio-chemotherapy, significantly increase long-term survival of oesophageal cancer patients.[18] The additional radio-chemical damage to the lungs, however, increases the mortality of post-oesophagectomy ARDS further, to almost 50%.[18]

Many attempts have been made to improve the outcome after ARDS by administering various inhibitors of mediators of inflammation to patients at

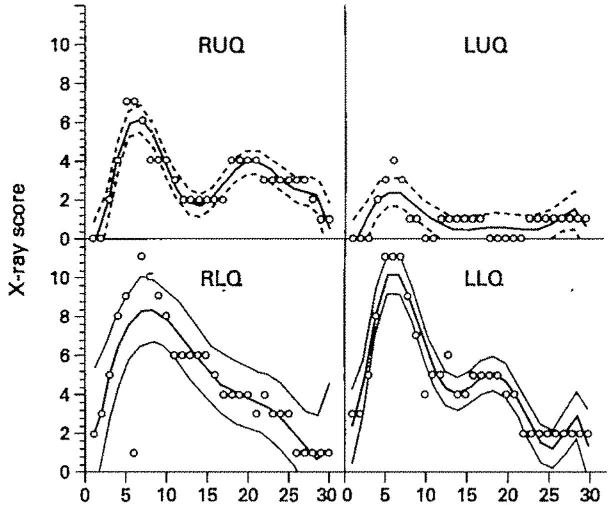

Figure 2 Summarized x-ray scores for six patients who developed ARDS after oesophageal resection (calculated according to Murray and colleagues[16]). The different points represent the summarized x-ray score on the given days. Broken lines = 95% confidence interval around the regression curve. RUQ = Right upper quadrant, RLQ = right lower quadrant, LUQ = left upper quadrant, LLQ = left lower quadrant.

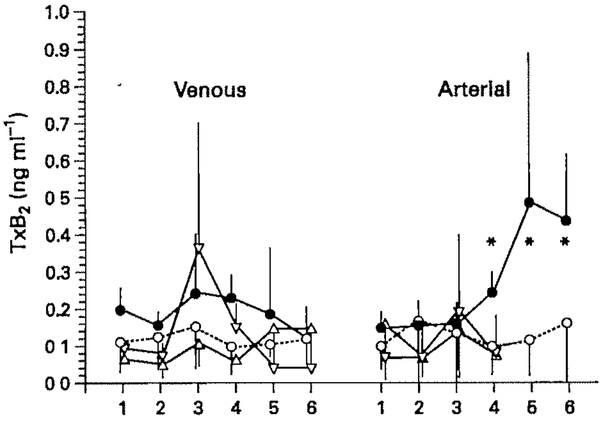

Figure 3 Concentrations of thromboxane B$_2$ (TxB$_2$) in patients who developed ARDS after oesophageal resection (n = 6, filled circles), without clinical signs of ARDS (n = 12, open circles), and in patients who underwent pneumonectomy (n = 6, open triangles) or lobectomy (n = 5, open inverted triangles). 1 = Before operation, 2 = before thoracotomy or transhiatal oesophageal mobilization, 3 = closure of thoracotomy or end of transhiatal oesophageal mobilization, 4 = end of surgery, 5 = postoperative day 1, 6 = postoperative day 2. $*P < 0.05$ compared with patients undergoing oesophagectomy not developing ARDS.

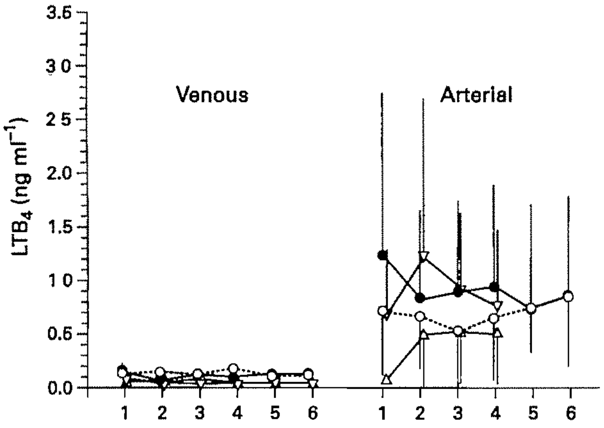

Figure 4 Concentrations of leukotriene B$_4$ (LTB$_4$) in patients after oesophageal resection who developed ARDS (n = 6, filled circles), without clinical signs of ARDS (n = 12, open circles), and in patients who underwent pneumonectomy (n = 6, open triangles) or lobectomy (n = 5, open inverted triangles). 1 = Before operation, 2 = before thoracotomy or transhiatal oesophageal mobilization, 3 = closure of thoracotomy or end of transhiatal oesophageal mobilization, 4 = end of surgery, 5 = postoperative day 1, 6 = postoperative day 2.

risk; however, only few randomized, double-blind, clinical studies have demonstrated improved patient survival.[1] When ketoconazole, a thromboxane A$_2$ synthetase inhibitor, was given to patients at risk of developing ARDS, on admission to the ICU, it appeared to lower the incidence of ARDS and reduce the mortality rate.[1] Experimental studies, however, repeatedly demonstrated beneficial effects of various inhibitors on the incidence or survival of ARDS. In these experiments, healthy animals were exposed to standardized insults and therapy was usually started before or shortly after the insult, which is rarely possible in clinical situations. The main reason for the lack of success in preventing ARDS in high-risk patients therefore appears to be the late start of therapy at a time when cellular responses to the humoral mediators have already been triggered. Patients undergoing oesophagectomy for oesophageal cancer are unusual in this respect and somehow resemble experimental conditions. They are a uniform group and develop ARDS predictably in 10–30% of cases.[7] Furthermore, the triggering insult is an elective surgical procedure which offers the opportunity to treat patients prophylactically, that is before any cascade systems of ARDS have been activated.

Several products of arachidonic acid metabolism are known to be involved in the development of ARDS, both in humans and animals. In this study we measured two metabolites of this cascade, TxB$_2$ (the stable metabolite of TxA$_2$) and LTB$_4$. Both have been shown to be increased in ARDS.[9] [20] Inhibitors of both mediators are available and one has been found to significantly decrease the incidence and mortality of ARDS, both in animals and humans.[1] [11] [12] In patients developing ARDS after oesophagectomy, we found increased concentrations of TxB$_2$, but not LTB$_4$, at the end of surgery, before the clinical appearance of ARDS. Interestingly, TxB$_2$ was increased only in post-pulmonary, but not in pre-pulmonary blood indicating that the lung was the source of thromboxane. Zheng and colleagues suggested that neutrophils, possibly activated by endotoxin,[21] might be the source of thromboxane in ARDS patients. Thromboxane is known to stimulate CD18 facilitated adhesion of neutrophils to pulmonary endothelial cells much more than to other endothelial cells.[22] This may lead subsequently to leucocyte margination, sequestration, adhesion, capillary leakage and pulmonary oedema. Furthermore, thromboxane is a potent vasoconstrictor and procoagulant.[9] It significantly increases pulmonary arterial pressure and causes formation of pulmonary microthrombi, which are known to occur in association with ARDS.[23] [24] In addition, pulmonary endothelial cells have been identified as a rich source of pro-inflammatory eicosanoids.[19]

Patients subjected to pulmonary resection had no increase in thromboxane concentrations despite undergoing thoracotomy and one-lung ventilation in a manner similar to patients admitted for oesophageal resection. This indicates a causative effect unique to oesophagectomy. In an experimental study, Ohwada and colleagues were able to prevent the development of post-oesophagectomy ARDS by preserving vagal nerve branches to the lung,[25] and pulmonary hypertension and bronchoconstriction induced by mediators of ARDS were reversible by stimulation of vagal nerves.[26] While contusion of the lung during pulmonary resection might well cause injury, preservation of vagal branches during lobectomy could prevent the increase in extravascular water associated with the clinical picture of ARDS. In contrast, resections of oesophageal malignancies require high cervical vagal nerve resection for oncological reasons.

Increased serum concentrations of endotoxin in patients undergoing oesophagectomy might be another explanation for the development of post-oesophagectomy ARDS. Endotoxin has been shown to be increased in patients with oesophageal carcinoma before and during surgery,[27] but no such findings have been reported for patients undergoing pulmonary resection for lung cancer. Acute lung injury in patients undergoing oesophagectomy might be a response to a second hit phenomenon, that is increased serum concentrations of endotoxin in the presence of surgical lung trauma.

Leukotrienes, potent chemoattractants and coactivators of neutrophils[22] are increased in bronchial fluid and serum of patients with ARDS, but appear to have no predictive value for the development of ARDS.[10] Our study appeared to confirm this finding as no significant changes in serum LTB_4 were found in any patient during the intraoperative and early postoperative course.

In summary, the association of increased thromboxane A_2 concentrations and the development of ARDS does not exclude other possible causes of ARDS but is consistent with the hypothesis that thromboxane A_2 may have an important role not only in sepsis and trauma, but also in patients developing ARDS after oesophageal resection. The early increase of thromboxane during surgery in arterial blood, but not in central venous blood, suggests that thromboxane originates from the lungs and its synthesis is probably initiated by surgical trauma. The unusual opportunity that oesophagectomy offers for preventive therapy of ARDS should encourage investigators to perform clinical studies in patients undergoing oesophageal resection caused by oesophageal carcinoma using some of the clinically available inhibitors of thromboxane synthesis.

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Endogenous source of bacteria in tracheal tube and proximal ventilator breathing system in intensive care patients

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Summary

Although bacteria from both the ventilator breathing system and the gastrointestinal tract have been implicated in the pathogenesis of ventilator-associated pneumonia, an endogenous source of bacteria in the proximal respiratory breathing system has yet to be demonstrated conclusively. We investigated a potential route of bacterial colonization from the stomach contents to the efferent limb of the ventilator breathing system by bacterial culture of daily specimens from six sites in 20 surgical intensive care patients. Gram-negative bacilli were isolated in a progressively increasing proportion of samples at successive sampling points, consistent with an endogenous-to-external route of spread (patients, chi-square = 14.12, $P < 0.02$; samples, chi-square = 106.15, $P < 0.001$). Identical strains of gram-negative bacilli, confirmed by REPS typing, were found at two or more sites in seven patients. In all seven, gram-negative bacilli were first isolated from a site in the patient. In none of the 20 patients was there evidence of a sequence of colonization from the ventilator tubing or Y-piece connector towards the patient. Probable colonization sequences plotted from the time of first isolation supported the proposed sequence in six patients, and in five began with the stomach contents. Isolation sequences contrary to the proposed direction of colonization involved four bacterial species and two patients, and did not extend beyond two sample sites. These findings imply that the retrograde route of bacterial colonization of the ventilated lung extends into the proximal respiratory breathing system and may help to identify additional targets for preventive intervention. (*Br. J. Anaesth.* 1998; **80**: 41–45)

Keywords: infection, nosocomial; intensive care; ventilation, mechanical; infection, bacterial; infection, breathing systems; equipment, breathing systems

Despite a substantial body of evidence implicating bacteria in the gastrointestinal tract as the cause of ventilator-associated pneumonia,[1–9] the role of bacteria in the stomach contents remains controversial.[10] The route followed by these bacteria during their initial entry into and colonization of the lower respiratory tract is an important consideration in preventive strategies designed to prevent ventilator-associated pneumonia.[11–13] Any new insight into this series of bacteriological events would thus be expected to have major implications for the preventive management of the critically ill.

We proposed previously that bacteria from the biofilm on the luminal surface of the tracheal tube might be disseminated into the lungs during the inspiratory phase of mechanical ventilation.[14] Further studies on the static and dynamic properties of tracheal tube biofilm in tubes from intensive care patients support the occurrence of fluid dynamic events in the tracheal tube and other parts of the proximal respiratory breathing system,[15 16] but bacteria in the luminal biofilm and their subsequent dissemination within the proximal breathing system have yet to be linked to a gastrointestinal source.

In this study, we have examined a possible retrograde route of bacterial transfer from the stomach via the tracheal tube to the efferent tubing in intensive care patients undergoing mechanical ventilation.

Patients and methods

Entry to the study was by consecutive admission to the adult surgical intensive care unit (ICU) of a tertiary referral hospital. Selection criteria were a requirement for mechanical ventilation at the time of ICU admission and access to stomach contents by nasogastric tube. Admission and clinical progress data were collected without reference to laboratory results. Tracheal suction was applied by nursing staff using single use suction catheters, and a gloved-hand technique. In-line, enclosed suction devices were not used during this study. Ventilator filters were not placed between the Y-piece connector and the ventilator tubing during the study.

SPECIMENS

A complete specimen set was obtained early every morning, 7 days a week, until the patient died or no longer required mechanical ventilation. All specimens were collected by the same investigator (T. J. J. I.) after preparing specimen containers, undergoing a

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thorough hand wash with chlorhexidine solution, and drying and donning of sterile gloves. The ventilator was then inactivated under the guidance of a member of the intensive care staff for the short time required to obtain bacteriological swabs. The sequence of specimen collection was in the opposite direction to the putative colonization sequence (i.e. from expiratory trap to stomach contents) in order to avoid bias caused by accidental carryover.

The ventilator trap in the expiratory limb of the ventilator tubing was disconnected briefly and a sterile dry cotton swab run around the inner circumference of the afferent limb of the trap. The Y-piece connector was then sampled, after disconnecting from the angle piece, by running a sterile dry cotton swab around its inner circumference. Next, the angle piece was removed briefly from the top of the tracheal tube and a dry, sterile cotton swab inserted without touching any surface other than the inside of the access port plug. A sterile swab was then run around the luminal circumference of the upper end of the tracheal tube. The connections and positioning of tubing were checked, and the ventilator cycle restarted. A specimen of gastric contents was obtained with a sterile 50-ml syringe via the nasogastric tube, after first discarding a smaller 10-ml syringe containing 5 ml or more of nasogastric tube contents. The previously used (early morning) tracheal suction catheter was kept for analysis by the attending intensive care nurse, who wrapped the catheter in her glove by turning the glove inside out during final removal. This specimen was placed in a self-seal bag, labelled and stored in the ICU specimen refrigerator if the other specimens had yet to be collected.

BACTERIOLOGICAL METHODS

Specimens were obtained for processing the same morning, other than those collected during weekends which were stored at 0–4 °C until the following Monday. Specimen recording, processing and further analytical work were performed without reference to clinical data. All results were withheld until after completion of the specimen collection phase of the study.

Each specimen was inoculated onto a single pre-prepared 5% horse blood agar 8-cm plate and an 8-cm MacConkey agar plate (Becton Dickinson, Heidelberg, Australia). Cotton swabs were applied and the inoculae spread following the conventional pattern. The lowermost 5 cm was cut from the tip of the tracheal suction catheter onto the blood agar plate using heat sterilized scissors, rolled to make a square impression. This was repeated on a MacConkey plate. The gastric contents specimen was mixed by repeated inversion and a 0.1-ml aliquot transferred by sterile pipette to the surface of the agar plate and spread with a sterile wire loop in the conventional manner. All plates were incubated for 18 h at 37 °C in air before examination. Any growth of gram-negative bacteria was noted and the colony isolated was identified to species level using standard methods.[17] Antibiotic susceptibility testing was performed on all isolates using the Kirby–Bauer method and NCCLS interpretation criteria.[18] Each isolate was stored by suspension in proprietary broth containing sterile beads (Microbank, USA) and frozen at −70 °C.

Molecular typing of isolates was performed on isolates resuscitated from the frozen culture collection by REP (repetitive extragenic palindromic) sequence analysis, as described previously,[9 19] but having adapted the method for use in capillary tubes with the rapid air thermal cycler.[20] Briefly, bacterial isolates were cultivated on nutrient agar at 37 °C for 48 h. A single colony of each isolate was picked off with a sterile toothpick and emulsified in 50 µl of sterile distilled water. The suspension was boiled for 5 min and then cooled on ice. A PCR mastermix was prepared in a laminar flow cabinet from 18 µl 10 × PCR reagent buffer (Promega, Madison, WI, USA), 18 µl of dNTPs 2 mmol litre^{-1} (Promega), 18 µl of 10% Triton X100 (Sigma Chemical Co., St Louis, MO, USA), 18 µl of sterile bovine serum albumin (Idaho Technology, Idaho Falls, ID, USA), 18 µl of dimethyl sulphoxide (E Merck, Darmstadt, Germany), 18 µl of $MgCl_2$ 10 mmol litre^{-1} (Idaho Technology), 18 µl of sterile distilled water, 25.2 µl of REP1-RI primer (5'IIIICGICGICATCIGGC-3', 500 mmol litre^{-1} stock solution) (Biosynthesis, Lewisville, KY, USA), 25.2 µl of REP2-I primer (5' ICGICTTATCIGGCCTAC-3', 500 mmol litre^{-1} stock solution) (Biosynthesis) and 18 ml of Taq DNA polymerase (8 µl of 5 u. ml^{-1} stock and 12 µl of enzyme diluent, Promega). Mastermix (10 µl) was dispensed into each pre-labelled sterile 1.5-ml Eppendorf tube, to which was added 1.2 µl of template DNA. After mixing, the reagents were drawn into a capillary reaction tube, the ends of which were heat sealed. The air thermal cycler (Idaho Technology) was programmed to run as follows: initial denaturation for 3 min at 95 °C, then 35 cycles of denaturation 0 min at 90 °C, annealing 1 min at 45 °C and elongation 8 min at 65 °C, with a final elongation at 65 °C for 16 min. Capillaries were then scored with a sapphire cutter and the contents dispensed into pre-labelled 1.5-ml Eppendorf tubes: 2-µl 5 × running buffer and dye were added to each tube and pipette mixed, and 12 µl of molecular marker (DNA 100 base pair ladder, Promega) and buffer were dispensed into the first of 15 wells in a 1% agarose (Sigma Chemical Co., St Louis, MO, USA) submarine gel, under Tris EDTA buffer. The amplified PCR product and buffer were dispensed into the remaining 14 wells and run at 100 V for 1.5 h. Staining was performed with ethidium bromide and visualization was with an ultraviolet transilluminator. The gel was photographed using Polaroid 667 film.

ANALYSIS

Isolates from different sites in the same patient, or the same site on different days, were regarded as possibly identical if the biochemical profile identified the same species, and antibiotic susceptibility differed by no more than one result. Isolates were referred to as identical only when amplified REP sequences produced an identical pattern on agarose gel electrophoresis. Identical first isolates from a given sample site were then plotted against the day the respective sample was collected.

Table 1 Patient characteristics (mean (range) or number)

n	20
Sex (M/F)	13/7
Admission category	
Neurosurgical—trauma	5
Neurosurgical—other	3
Abdominal	6
Thoracic	2
ENT	1
Orthopaedic—trauma	1
Other	2
Age (yr)	54.9 (21–91)
APACHE score	15.6 (3–32)
Days in study	5.25(2–18)

STATISTICAL METHODS

The chi-square test was calculated using epidemiological software (C-stat, version 1.0, Cherwell Scientific, Oxford, UK) running under DOS 5.0. A threshold *P* value of 0.05 was used in assessments of statistical significance.

Results

Twenty consecutive patients admitted to the surgical intensive care unit were investigated (patient and clinical data are shown in tables 1 and 2). The proportion of patients and specimens from which gram-negative bacilli were isolated increased at successive sampling points in the specimen sequence followed (table 3). In seven patients and 12 series of isolates, gram-negative bacilli from more than one specimen site were identical by REP sequence analysis (table 4). In all seven patients and 12 bacterial series, the first isolate was obtained from a site within the patient, and in all but five instances the temporal sequence of isolation of a given REP sequence pattern was consistent with the proposed luminal route of bacterial colonization. However, in four series of identical bacterial isolates (three from one patient), isolates from the suction catheter tip or tracheal tube lumen antedated isolation of the same strains from the stomach contents. In one other patient, first isolation was at the angle piece and was followed by isolation from the suction catheter tip. No confounding colonization sequence involving more than two adjacent sites was observed.

Discussion

In this study of bacterial colonization in patients undergoing mechanical ventilation, the source of gram-negative species contaminating the proximal respiratory breathing system was the patient in every case where identical gram-negative bacilli were isolated from two or more specimen sites. There was no evidence to support progression of bacteria from the ventilator, or even carryover during the sampling procedure. On the contrary, the significant increase in gram-negative bacilli at successive sampling points implied that a colonization sequence that started in the ventilator tubing was unlikely, and was consistent with a progressive colonization of luminal surfaces in the opposite direction. In the majority of bacterial isolate series, the time of first isolation at a given site was consistent with the proposed luminal route of bacterial transfer, that is from the stomach contents via the oesophagus, into the trachea, down the outside of the tracheal tube and, on the suction catheter up into the tracheal tube, from where spread to the angle piece connector, the bifurcation of the Y-piece and finally the expiratory tubing could occur.

We did not attempt to determine if the oropharynx acted as a portal of entry, a secondary source of bacteria or a staging post in retrograde colonization, as resolution of the role of the oropharynx would have required sampling at multiple intra-oral sites. Instead, the study aimed to give equal prominence to the six locations sampled and to use rigorous bacteriological criteria to exclude similar but non-identical isolates. Inclusion of a genetic typing method in the assessment criteria necessitated exclusion of several possible isolate series, permitting a greater degree of confidence in the postulated colonization sequence.[21]

In five (25%) of the patients studied the gram-negative species concerned were observed first in the stomach contents. However, in two other patients the bacteria appeared first on the suction catheter tip, several days before the stomach contents. We have shown previously that gastric bacterial overgrowth may be intermittent in intensive care patients[22] but it remains possible that the gastric contents were contaminated by bacteria from the oropharynx, prior

Table 2 Patients studied; clinical data

Patient No.	Reason for ICU admission	Concurrent disease	Antibiotics at ICU admission	Duration of intubation
1	Shock	Myocardial infarction, intracranial haemorrhage	Vancomycin	8 days
2	Subtotal hepatectomy	Hepatocellular carcinoma	Ceftriaxone, metronidazole	36 h
3	Septic shock	Intestinal perforation	Gentamicin, co-amoxyclav	19 days
4	Shock	Gastric carcinoma, leaking anastomosis	Ciprofloxacin, vancomycin	15 days
5	Perforated gastric ulcer	Cardiorespiratory failure	Amikacin, metronidazole	2 days
6	Head injury, multiple fractures		Cloxacillin, metronidazole	4 days
7	Head injury		Cefazolin	7 days
8	Total gastrectomy	Perforated DU	Ceftriaxone	4 days
9	Craniotomy	Extradural haematoma	Nil	36 h
10	Craniotomy	Brainstem haemangioma	Cefazolin	36 h
11	Craniotomy	Haematoma evacuation	Cefazolin	14 days
12	Laparotomy	Peritonitis, ruptured appendix	Ceftriaxone	24 h
13	Cardiac and renal failure	Ischaemic heart disease	Nil	2 days
14	Craniotomy	Subarachnoid haemorrhage	Ceftriaxone	2 days
15	Obstructed airway	Ludwig's angina	Ciprofloxacin	3 days
16	Septic shock	Diabetes, renal failure	Imipenem, fluconazole	2 days
17	Septic shock	Mesenteric embolus, bronchial asthma, ischaemic heart disease	Ceftriaxone, metronidazole	2 days
18	Head injury	Aspiration	Gentamicin, metronidazole, ampicillin	7 days
19	Oesophageal surgery	Hepatic cirrhosis, portal hypertension	Cefuroxime	2 days
20	Head injury		Cephazolin	2 days

Table 3 Patients and specimens from which gram negative bacilli (GNB) were isolated. ET=Expiratory trap, YP=Y-piece, AP=angle piece, TTL=tracheal tube lumen, SCT=suction catheter tip, GA=gastric aspirate. *Chi-square=14.12, df=5, $P<0.02$;†chi-square=106.15, df=5, $P<0.001$

	Patients*		Specimens†		First isolated (day)	
Site	No GNB	GNB(%)	No GNB	GNB(%)	Range	Median
ET*	15	5 (25)	85	8 (9)	1–9	5.0
YP	15	5 (25)	83	10 (11)	4–9	7.0
AP	14	6 (30)	78	14 (15)	1–9	3.5
TTL	9	11 (55)	63	30 (32)	1–8	2.0
SCT	7	12 (63)	35	53 (60)	1–4	1.0
GA	7	12 (63)	40	44 (52)	1–6	1.0

Table 4 Series of identical bacterial isolates from intensive care patients and their corresponding respiratory breathing system. GA=Gastric aspirate; SCT=suction catheter tip; TTL=tracheal tube lumen; AP=angle piece connector; YP=Y-piece; ET=expiratory trap. Numbers represent day of specimen collection

	GA	SCT	TTL	AP	YP	ET
Patient A						
Escherichia coli	6	1	4			
Citrobacter diversus	7	1				
Acinetobacter baumannii	8	2	4	7		10
Patient B						
Citrobacter diversus	3	1				
Patient C						
Enterobacter aerogenes	2	8			9	
Klebsiella pneumoniae		2		2		9
Acinetobacter baumannii		6				9
Enterobacter cloacae		6		2		
Patient D						
Acinetobacter baumannii	1	2				
Patient E						
Acinetobacter baumannii	1	1	2		4	
Patient F						
Enterobacter cloacae	1	1		4		
Patient G						
Klebsiella pneumoniae	1	1				

gram-negative colonization at this site being common in hospitalized patients.[23] In two patients more than one gram-negative species followed the proposed colonization pathway. As the same phenomena appear to occur with different bacterial genera, much of the process of bacterial transfer from site to site could be explained by movement of fluids within the lumina of anatomical structures or respiratory devices.

Our observations are consistent with previous findings that the patient's end of the ventilator breathing system is more likely to be contaminated by gram-negative bacilli.[24] Moreover, these findings would suggest that the bacteria observed on the luminal surface of the tracheal tube originated in the patient's endogenous flora; either in the stomach contents, or possibly the oropharynx. If this is indeed the case, the suction catheter must be considered a means of transferring these bacteria and the other components of tracheal tube biofilm from the tracheal mucosa to the inside of the tracheal tube.[15] The subsequent dissemination of bacteria-laden particles from the luminal biofilm has to be inferred,[14 16] as direct observation is not possible *in vivo*.

The first point in the expiratory gas pathway that could act as an inertial impaction filter to trap aerosolized bacteria is where expired gases negotiate a 90° change in direction at the angle piece connector. The inner surface of the angle piece connector, where angle piece swabs were obtained, was therefore chosen as the most likely location for bacterial deposition after aerosolization of tracheal tube biofilm during the expiratory phase of ventilation. The presence of gram-negative bacteria on the inside of the angle piece in two isolate series after only 2 days, without identical isolates on the luminal surface of the adjacent tracheal tube, would therefore be consistent with aerosolization of bacteria during the expiratory phase of ventilation. Bacterial contamination of additional locations in the proximal respiratory breathing system prone to high velocity turbulent flow during the inspiratory phase of mechanical ventilation would be expected to increase the risk of dissemination of a bacteria-laden aerosol into the patient's lungs. The angle piece may have been a point of entry for bacteria subsequently isolated from the trachea in one case. If so, this may represent an isolated occurrence of exogenous colonization.

We have identified a possible route of bacterial colonization from the stomach via the tracheal tube and onwards into the ventilator breathing system. The results presented here prompt several important questions, particularly regarding the interaction between the suction catheter, tracheal secretions and the luminal surface of the tracheal tube. The extension of the so-called "retrograde" route of bacterial colonization of the ventilated lung proposed here should lead to additional target sites for preventive interventions, if our provisional conclusions are confirmed in further studies using other cohorts of intensive care patients.

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Analysis of the EEG bispectrum, auditory evoked potentials and the EEG power spectrum during repeated transitions from consciousness to unconsciousness

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Summary

We have compared the auditory evoked potential (AEP) index (a numerical index derived from the AEP), 95% spectral edge frequency (SEF), median frequency (MF) and the bispectral index (BIS) during alternating periods of consciousness and unconsciousness produced by target-controlled infusions of propofol. We studied 12 patients undergoing hip or knee replacement under spinal anaesthesia. During periods of consciousness and unconsciousness, respective mean values for the four measurements were: AEP index, 60.8 (SD 13.7) and 37.6 (6.5); BIS, 85.1 (8.2) and 66.8 (10.5); SEF, 24.2 (2.2) and 18.7 (2.1); and MF, 10.9 (3.3) and 8.8 (2.0). Threshold values with a specificity of 100% for a state of unconsciousness were: AEP index, 37 (sensitivity 52%); BIS, 55 (sensitivity 15%); and SEF, 16.0 (sensitivity 9%). There was no recorded value for MF that was 100% specific for unconsciousness. Of the four measurements, only AEP index demonstrated a significant difference ($P < 0.05$) between all mean values 1 min before recovery of consciousness and all mean values 1 min after recovery of consciousness. Our findings suggest that of the four electrophysiological variables, AEP index was best at distinguishing the transition from unconsciousness to consciousness. (*Br. J. Anaesth.* 1998; **80**: 46–52)

Keywords: brain, evoked potentials; monitoring, evoked potentials; monitoring, electoencephalography; monitoring, depth of anaesthesia; anaesthesia, depth

The ability to detect recovery of consciousness from a state of unconsciousness is an essential attribute for a monitor of depth of anaesthesia so that awareness during anaesthesia may be prevented. While an ideal method of assessment of anaesthetic depth remains an elusive goal, it has been suggested that monitoring of auditory evoked potentials (AEP)[1–3]or bispectral electroencephalographic (EEG) analysis[4–8] may be more reliable than other techniques. Recently, the AEP index (formerly known as the level of arousal score), a mathematical derivative which reflects AEP waveform morphology that is calculated from the amplitude difference between successive segments of the AEP curve,[9] has been investigated as a means of assessment of depth of anaesthesia.[10–12] Median frequency (MF)[13 14] and 95% spectral edge frequency (SEF)[7 15] of the EEG power spectrum have also been investigated for assessing anaesthetic depth and have been incorporated into commercially available monitors for this purpose.

In a recent study, our group observed that while the bispectral index (BIS) and to a lesser extent SEF correlated well with predicted blood concentrations of propofol during recovery from anaesthesia, AEP index was best at distinguishing consciousness from unconsciousness.[16] Therefore, this study was designed to investigate further the ability of AEP index, BIS, SEF and MF to identify awareness by their capacity to detect recovery of consciousness. We assessed changes in these electrophysiological measurements during alternating periods of unconsciousness and consciousness, the reproducibility of these changes in each patient and analysed the amount of inter-patient variability.

Patients and methods

After obtaining hospital Ethics Committee approval and informed consent, we studied 12 patients undergoing orthopaedic surgery (hip or knee replacement) under spinal anaesthesia. Two male patients and 10 female patients, mean age 73.8 (range 62–82) yr and mean weight 70.7 (55–84) kg completed the study. Patients with psychiatric or hearing abnormalities were excluded.

All patients were premedicated with temazepam 30 mg, 2 h before surgery. Spinal anaesthesia was produced with either 0.5% plain bupivacaine 3.0–3.5 ml or 0.75% plain bupivacaine 3 ml administered via a 26-gauge needle at the L2–3 interspace. An extradural catheter was also inserted for administration of top-up doses during surgery in prolonged cases.

After ensuring adequate regional anaesthesia for surgery, a target-controlled infusion (TCI)[17] of propofol was commenced and oxygen administered via a nasal sponge. One anaesthetist was responsible for standard monitoring of the patient and for manipulating the TCI of propofol to produce alternating periods of consciousness and uncon-

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sciousness. Two investigators were present in addition to the anaesthetist responsible for conducting the anaesthetic. One investigator observed the AEP system and the EEG monitor, and recorded the timing of events such as onset of unconsciousness and consciousness. At intervals of 30 s, the second investigator established the presence or absence of an eyelash reflex and the patient's response to a verbal command to squeeze the investigator's hand. The transition from consciousness to unconsciousness was defined as the point at which loss of response to verbal command occurred, and the return of this response was considered the transition from unconsciousness to consciousness.

AUDITORY EVOKED POTENTIAL MONITORING

Auditory evoked potentials were monitored as described in our previous studies.[16 18] The EEG was obtained from three disposable silver–silver chloride electrodes (Zipprep, Aspect Medical Systems, USA) placed on the right mastoid (+), and middle forehead (−), with Fp_2 as the reference. The custom-built amplifier had a 5-kV medical grade isolation, common mode rejection ratio of 170 dB with balanced source impedance, input voltage noise of 0.3 μV and current input noise of 4 pA (0.05 Hz–1 kHz rms). A third-order Butterworth analogue band-pass filter with a bandwidth of 1–220 Hz was used. The auditory clicks were of 1 ms duration and 70 dB above the normal hearing threshold. They were presented to the right ear at a rate of 6.9 Hz. The amplified EEG was sampled at a frequency of 1778 Hz by a high accuracy, low distortion 12-bit analogue-to-digital converter (PCM-DAS08, Computer Boards Inc., USA) and processed in real-time by a microcomputer (T1950CT, Toshiba, Japan).

AEP were produced by averaging 256 sweeps of 144 ms duration. The time required for a full update of the signal was 36.9 s, but a moving time averaging technique allowed a faster response time to any change in the signal. Averaged curves were obtained at 3-s intervals.

The AEP index, which reflects the morphology of the AEP curves, allowed on-line analysis of the AEP. It is calculated as the sum of the square root of the absolute difference between every two successive 0.56-ms segments of the AEP waveform.[9] The AEP and other data were stored automatically on the hard disk of the microcomputer every 3 s, enabling future retrieval for further analysis.

EEG BISPECTRAL AND POWER SPECTRAL ANALYSIS

The EEG was obtained from four Zipprep electrodes placed on both sides of the outer malar bone (At_1 and At_2) with Fpz as the reference and Fp_1 as the ground. The EEG bispectrum, SEF and MF were monitored using a commercially available EEG monitor (A-1000, BIS 3.0 algorithm, rev. 0.40 software, Aspect Medical Systems, USA). The update rate on the bispectral index monitor was set to 10 s with the bispectral smoothing function switched off. Data from the A-1000 EEG monitor were down loaded automatically and stored on the microcomputer every 5 s.

Both monitoring systems (AEP and EEG) had sophisticated artefact rejection algorithms and the amplifiers of both also had medical grade isolation. Furthermore, the auditory clicks that produced the AEP generate signals 100 times smaller than the remainder of the EEG. Therefore, although the AEP and EEG were monitored simultaneously, there would have been no interference between the two systems that could have affected the results.

DATA ANALYSIS

Periods of consciousness and unconsciousness extended between the time of recovery of consciousness (response to verbal command) and the time when consciousness was lost (loss of response to verbal command). However, the periods from 1 min before until 1 min after transitions from one state of consciousness to the next were excluded when conscious and unconscious values of each measurement were analysed. These periods were excluded because they were likely to contain values representative of both consciousness and unconsciousness, as 36.9 s were required to obtain a full update of the AEP index (and 30 s for the BIS), and patients were also most likely to be drifting in and out of consciousness during these periods. Therefore, conscious values were considered to be those recorded during periods from 1 min after regaining consciousness until 1 min before the next loss of consciousness (fig. 1). Unconscious values were those recorded during periods from 1 min after loss of consciousness until 1 min before the next recovery of consciousness (fig. 1).

To investigate the ability of the electrophysiological variables to detect awareness, values recorded 1 min before recovery of consciousness were compared with values at 1 min after consciousness returned (fig. 1). All patients had at least three transitions from unconsciousness to consciousness. Therefore, the first three transitions were used to compare the ability of the different measurement systems to detect these transitions.

The mean (SD) and range of each measurement during all periods of consciousness and unconsciousness were determined by analysing all conscious and unconscious values, respectively, recorded over the course of the study. Measurements made during all periods of unconsciousness and consciousness were used to determine threshold values with 100% specificity and threshold values with approximately 85% sensitivity. Statistical analysis was with Minitab 10.5 for Windows, using ANOVA with Tukey's test. $P < 0.05$ was considered significant.

All patients were interviewed on the day after surgery for memory of intraoperative events. They were also questioned on their satisfaction with the auditory clicks and the technique of monitoring.

Results

Mean duration of surgery was 74 (range 58–121) min. There was a mean of 10 (6–20) periods of consciousness and unconsciousness.

AUDITORY EVOKED POTENTIAL INDEX

Table 1 shows the mean values for AEP index, BIS, SEF and MF recorded during all conscious or unconscious periods, as defined above. Table 2 shows

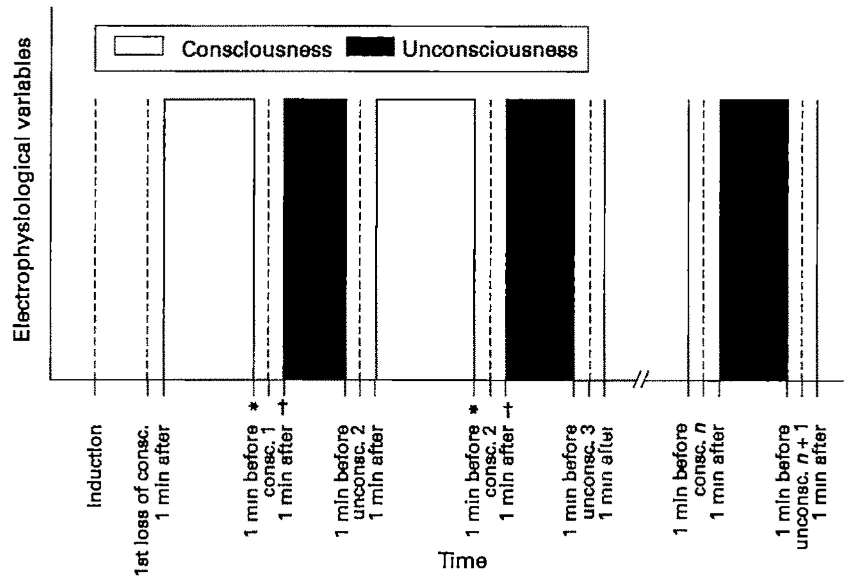

Figure 1 Periods when the four electrophysiological measurements (auditory evoked potential index (AEP index), bispectral index (BIS), spectral edge frequency (SEF) and median frequency (MF)) were analysed. All values recorded during periods of consciousness (consc.) and unconsciousness (unconsc.) were used to analyse the differences between the two states. Unconscious values of the four measurements at 1 min before regaining consciousness (*) were compared with conscious values at 1 min after regaining consciousness (†), at the first three transitions.

Table 1 Mean (range) values for the auditory evoked potential (AEP) index, bispectral index (BIS), 95% spectral edge frequency (SEF) and median frequency (MF) during consciousness (consc.) and unconsciousness (unconsc.)

	Unconsc.	Consc.
AEP index	37.6 (21–55)	60.8 (38–98)
BIS	66.8 (40–94)	85.1 (56–98)
SEF	18.7 (12.5–26.5)	24.2 (16.1–29.1)
MF	8.8 (1.7–13.7)	10.9 (1.5–18.9)

the threshold values of the four measurements with 100% specificity and threshold values with close to 85% sensitivity for states of consciousness and unconsciousness. In total, 4823 unconscious and 2055 conscious values of the AEP index, and 2885 unconscious and 1322 conscious values of BIS, SEF and MF were analysed. A threshold value of the AEP index of 37 had a specificity of 100% and a sensitivity of 52% for a state of unconsciousness. A threshold value of 56 was 60% sensitive and 100% specific for consciousness. Figure 2 shows the mean AEP index and BIS before and after the first three transitions from unconsciousness to consciousness. All mean awake values 1 min after return of consciousness were significantly higher than all mean unconscious values 1 min before ($P < 0.05$). AEP index values during periods of consciousness were more variable than values during unconsciousness (fig. 2, table 1).

Table 2 Values of the auditory evoked potential (AEP) index, bispectral index (BIS), 95% spectral edge frequency (SEF) and median frequency (MF) with 100% specificity and values with approximately 85% sensitivity for consciousness and unconsciousness

	Threshold	Sensitivity (%)	Specificity (%)
Unconscious			
AEP index	37	52	100
	44	85	87
BIS	55	15	100
	76	86	83
SEF	16.0	9	100
	21.0	85	92
MF	1.4	0	100
	10.7	85	55
Conscious			
AEP index	56	60	100
	45	87	85
BIS	95	14	100
	75	88	80
SEF	26.6	15	100
	21.9	84	92
MF	13.8	18	100
	7.9	85	25

BISPECTRAL INDEX

Table 1 shows that, unlike AEP index, some BIS values during unconsciousness were higher than the *mean* value during consciousness, and some conscious values were also lower than the *mean* value during unconsciousness. A BIS of 55 had a specificity of 100% but was only 15% sensitive for a state of unconsciousness (table 2). A very high value of 95 was required for 100% specificity for consciousness and was only 14% sensitive. Figure 2 shows the mean BIS at 1 min before and after the first three transitions from unconsciousness to consciousness. Unlike the AEP index, mean awake values 1 min after return of consciousness were not *all* significantly different from mean unconscious values 1 min before regaining consciousness ($P < 0.05$). BIS also contrasted with AEP index in that values recorded during unconsciousness demonstrated more inter-patient variability than values during periods of consciousness (table 1).

SPECTRAL EDGE FREQUENCY

Comparable with BIS but unlike AEP index, some SEF values during unconsciousness were higher than the *mean* value during consciousness, and some conscious values were lower than the *mean* value during unconsciousness (table 1). An SEF value of 16.0 Hz had a specificity of 100% but only 9% sensitivity for a state of unconsciousness (table 2). A value of 26.6 Hz was 100% specific but only 15% sensitive for

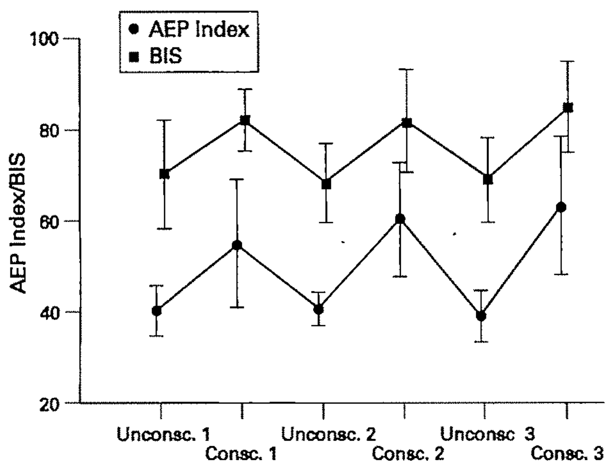

Figure 2 Mean (SD) auditory evoked potential (AEP) index and bispectral index (BIS) at 1 min before and after the first three transitions from unconsciousness (unconsc.) to consciousness (consc.). There was no significant difference between BIS at unconsc. 1 and consc. 2.

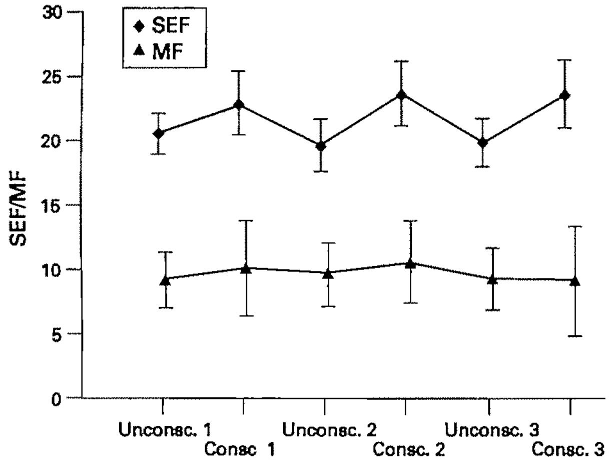

Figure 3 Mean (SD) spectral edge frequency (SEF) and median frequency (MF) at 1 min before and after the first three transitions from unconsciousness (unconsc.) to consciousness (consc.). There was no significant difference between SEF at unconsc. 1 and consc. 1.

consciousness. Figure 3 shows mean SEF and MF values at 1 min before and after the first three transitions from unconsciousness to consciousness. In common with BIS but unlike AEP index, mean awake values of SEF 1 min after return of consciousness were not *all* significantly different from mean unconscious values 1 min before regaining consciousness ($P < 0.05$). Similar to AEP index but unlike BIS, awake values of SEF were generally more variable than values recorded during periods of unconsciousness (fig. 3).

MEDIAN FREQUENCY

Similar to BIS and SEF, some values of MF during unconsciousness were higher than the *mean* value during consciousness, and some conscious values were lower than the *mean* value during unconsciousness (table 1). The lowest recorded awake value of MF was lower than the minimum MF value during unconsciousness (table 1) so that a value of 1.4 Hz, which was never attained, would have been 100% specific for unconsciousness (table 2). An MF value of 13.8 Hz was 100% specific but only 18% sensitive for consciousness. Figure 3 shows mean MF values at 1 min before and after the first three transitions from unconsciousness to consciousness. Although mean awake values of MF tended to be numerically greater than mean values during unconsciousness, all mean conscious and unconscious values were not significantly different. There was relatively large inter-patient variability for MF values during both consciousness and unconsciousness, and in common with AEP index and SEF but unlike BIS, this variability was greater during periods of consciousness (fig. 3).

No patient had recall of any event in theatre, including application of earphones and auditory clicks. All patients were satisfied with the anaesthetic technique and were happy to have the same technique of monitoring for any future anaesthetic.

Discussion

Although consistent changes (increased latency and decreased amplitude) in middle latency auditory evoked potential (AEP) waves occur as anaesthesia is deepened, it is difficult to analyse AEP waves in real time and to quantify changes in the clinical situation. The AEP index, a mathematical derivative that reflects AEP waveform morphology,[9] allows on-line assessment of the AEP during anaesthesia and surgery. Conventional EEG processing techniques such as those used to measure spectral edge frequency (SEF) and median frequency (MF) ignore the inter-frequency phase information in the EEG and may be unreliable for monitoring the level of anaesthesia because of the variable effects produced by different anaesthetic agents and the large inter-patient variability.[19] Unlike power spectrum analysis, bispectral EEG analysis also quantifies the phase coupling between component EEG frequencies.[20] The bispectral index (BIS), a numerical value derived from the EEG bispectrum, has been shown to have characteristics desirable in an anaesthetic depth monitor, such as the capacity to predict movement in response to surgery[4 21] and to detect consciousness[22-24] when using a variety of anaesthetic drugs.

The ability to distinguish consciousness from unconsciousness is an essential feature of a monitor of depth of anaesthesia, and was the clinical end-point used in this study, circumventing the problem of the absence of a universally accepted standard by which to compare such monitors under investigation.

The assumption that awareness, and therefore consciousness, is indicated by a response to command has been made in previous studies.[25 26] However, intraoperative awareness may occur without postoperative recall,[27] as occurred in all of our patients. Nevertheless, prevention of the dreaded consequence of intraoperative awareness without amnesia, especially in the presence of inadequate analgesia, is one of the most important functions of anaesthetic depth monitors. Amnesia for intraoperative events may have occurred in our patients because of the use of benzodiazepine premedication[28] or general anaesthetic drugs.[29 30]

Our study demonstrated the potential of the AEP index to detect recovery of consciousness. Of the four electrophysiological variables studied, only AEP

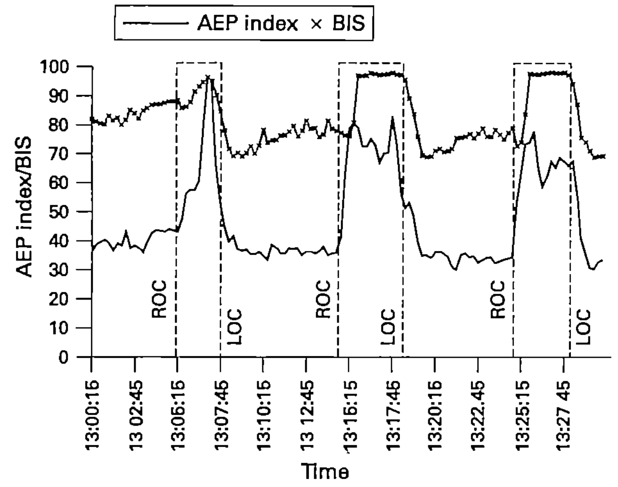

Figure 4 Changes in auditory evoked potential index (AEP index) and bispectral index (BIS) at recovery of consciousness (ROC) and loss of consciousness (LOC) for one patient in this study.

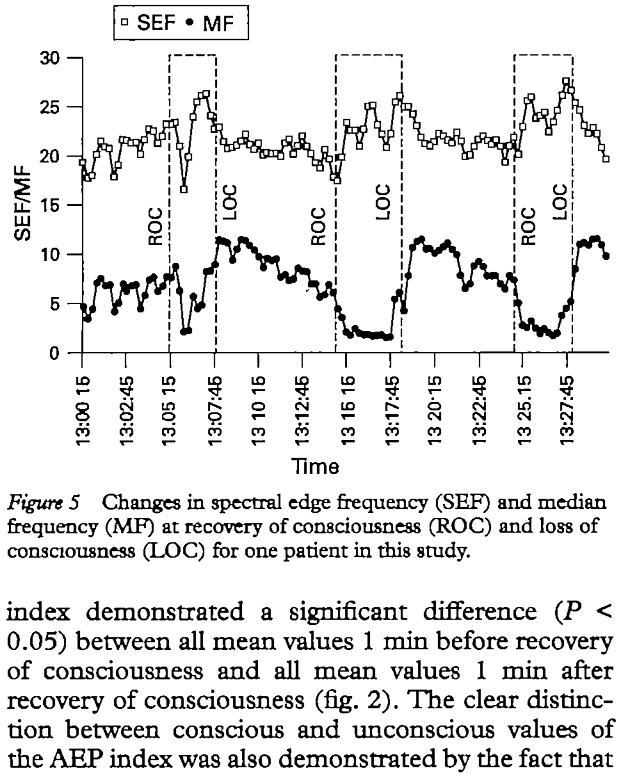

Figure 5 Changes in spectral edge frequency (SEF) and median frequency (MF) at recovery of consciousness (ROC) and loss of consciousness (LOC) for one patient in this study.

index demonstrated a significant difference ($P < 0.05$) between all mean values 1 min before recovery of consciousness and all mean values 1 min after recovery of consciousness (fig. 2). The clear distinction between conscious and unconscious values of the AEP index was also demonstrated by the fact that it was the only measurement in this study whose lowest recorded conscious value was higher than the mean unconscious value, and whose highest unconscious value was lower than the mean conscious score.

Although other studies[22-24] have shown BIS to be capable of detecting consciousness, in this study BIS was not significantly different when values 1 min before and after recovery of consciousness were compared. This could be explained by the gradual increase in BIS which frequently occurs during emergence from anaesthesia.[31 32] Values recorded 2 min apart (1 min before and after recovery) would therefore be more similar to each other than corresponding AEP index values, which increase suddenly at the time of awakening.[16] Figure 4, which shows changes in AEP index and BIS for one of the patients in our study, demonstrates this gradual increase in BIS during the first transition from unconsciousness to consciousness. In contrast, the AEP index increased sharply at all three transitions in this patient.

MF was least capable of distinguishing consciousness from unconsciousness, as all mean conscious and unconscious values were similar to each other (fig. 3). Studies by Schwilden and colleagues have suggested that MF values less than approximately 5 Hz indicate unconsciousness and that values of 2–3 Hz indicate a satisfactory depth of anaesthesia.[13 33-35] The difference between our findings and those of Schwilden and co-workers may be explained by differences in methodology and by the effects of EEG burst suppression which lead to misinterpretation of the EEG power spectrum.[36] In addition, there is possibly a lag between changes in MF and changes in anaesthetic concentration during recovery which could explain the *lower* values during conscious periods and *higher* unconscious values demonstrated in one of the patients in the present study (fig. 5).

The already low frequency of awareness during anaesthesia of 0.1%,[2 37] and the potentially disastrous consequences of its occurrence suggest that we should be attempting to develop monitors that will almost guarantee its elimination by reliably detecting unconsciousness. Such a monitor should be capable of providing information that is specific for unconsciousness at a level of anaesthesia that is not excessive. A BIS value of 55 was 100% specific but only 15% sensitive for unconsciousness (table 2). Additionally, a threshold value of 95 was necessary for 100% specificity for consciousness, as there were very high values of BIS recorded during periods of unconsciousness. These findings suggest that BIS could not be used to direct anaesthetic administration to *ensure* unconsciousness without the risk of excessive anaesthesia. Values of BIS which are specific for unconsciousness are not sensitive enough, and some adequately anaesthetized (clinically unconscious) patients have BIS values of fully awake subjects.

A similar problem of excessive anaesthesia may occur if SEF is used to ensure unconsciousness, as a value of 16.0 Hz was 100% specific but only 9% sensitive for unconsciousness. Very high SEF values were also recorded during unconsciousness so that a value of 26.6 Hz was necessary for 100% specificity for consciousness.

In contrast, an AEP index of 37 was 100% specific for unconsciousness, with a much greater level of sensitivity (52%) than corresponding SEF and BIS values. There was also no problem for unconscious patients with a very high AEP index, and a value of 56 was 100% specific and 60% sensitive for consciousness. These findings suggest that it may be possible to aim for an AEP index value that ensures unconsciousness while avoiding excessive anaesthesia.

The range of BIS values during periods of consciousness in this study varied between 68 and 98. Other studies have reported variable BIS values of approximately 50–85 at the time of recovery of consciousness.[8 16 22-24] Flaishon, Sebel and Sigl[23] reported that no unconsciousness was observed when BIS was greater than 70 and no consciousness occurred at values less than 65. In contrast, no consciousness was observed in this study at scores less than 55, while 36% of BIS values during unconsciousness (1048 of 2885 values) were greater than 70. The wide variation in BIS values between these studies may be a result of the use of different anaesthetic agents and different clinical end-points used to define consciousness.

Other studies have reported different results for SEF and MF during consciousness and unconsciousness. Median SEF was 20.4 Hz on recovery and 10.1 Hz during anaesthesia in one of the studies in Schwilden's series[35] compared with corresponding mean values of 24.2 and 18.7 Hz in this study. However, there was large variability in SEF values in both studies. Arndt, Hofmockel and Benad reported that adequate anaesthesia could be expected when SEF ranged from 14 to 16 Hz.[38] While an SEF value of 16 Hz was 100% specific for unconsciousness in our study (table 2), it was only 9% sensitive. Schwilden and colleagues also reported that no response to verbal command occurred at an MF value of less than 5 Hz for a variety of drugs.[33–35] In contrast, consciousness was present in the range 2–19 Hz in our study and, while 5 Hz was 94% specific for unconsciousness, it was only 7% sensitive.

This study demonstrated the potential of the AEP index to detect recovery of consciousness from propofol anaesthesia. Unconsciousness caused by different anaesthetic agents may produce dissimilar effects on the EEG[19 39 40] and on BIS,[21 41–44] although consistent changes have been demonstrated in MLAEP waves.[5 45–47] Further studies are therefore necessary to investigate the ability of these measurements to detect recovery of consciousness from anaesthesia produced by different drugs. Another limitation of this study was the lack of influence of surgical stimuli, effectively abolished by spinal anaesthesia, on the four measurements. Surgical stimulation is known to affect the EEG[48] and AEP.[48–50] However, it would be morally and ethically challenging to design a study in which consciousness was repeatedly induced in the presence of a painful surgical wound.

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Comparison of pirenzepine, ranitidine, and pirenzepine–ranitidine combination for reducing preoperative gastric fluid acidity and volume in children

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Summary

We conducted a two-part controlled study to evaluate the efficacy of preoperative oral pirenzepine (muscarinic receptor antagonist known to inhibit gastric secretion), ranitidine, and the combination pirenzepine–ranitidine in controlling gastric fluid pH and volume in 210 ASA I children, aged 2–14 yr, undergoing elective surgery. In the first part of the study ($n = 90$), the proportion of children considered at risk for aspiration pneumonitis was reduced with pirenzepine 25 mg ($P < 0.05$) but not with 12.5 mg. In the second part of the study, the other 120 children were allocated randomly to one of four groups: pirenzepine 25 mg with placebo; ranitidine 75 mg with placebo; pirenzepine 25 mg with ranitidine 75 mg; and placebo and placebo. These medications were administered 1 h before anaesthesia. After tracheal intubation, volume and pH of the gastric fluid aspiration via a multi-orifice orogastric tube were measured. Pirenzepine 25 mg decreased gastric fluid volume ($P <$ 0.05) but failed to increase gastric pH. Ranitidine 75 mg increased gastric pH ($P < 0.05$) but failed to decrease fluid volume. The pirenzepine–ranitidine combination reduced gastric fluid acidity and volume ($P < 0.05$). (*Br. J. Anaesth.* 1998; **80**: 53–57)

Keywords: pharmacology, pirenzepine; antacids, ranitidine; complications, aspiration; gastrointestinal tract, pH; gastrointestinal tract, volume; gastrointestinal tract, antimuscarinics

Paediatric general anaesthesia is associated with a risk of pulmonary aspiration gastric contents[1] and the incidence of this complication is higher than in adults.[2] Many children arriving in the operating theatre have been shown to have a gastric fluid volume >0.4 ml kg^{-1} and a pH <2.5, regardless of the fasting interval.[3–6] Patients who fulfill these criteria are believed to be at increased risk of developing aspiration pneumonitis.[7] Several pharmacological interventions have proved successful in reducing the risk of lung damage by controlling gastric acid secretion, including H_2 histaminergic receptor antagonists and proton pump inhibitors.[1,3–6,8–13]

Pirenzepine, a selective M1 muscarinic receptor antagonist,[14] has been used extensively as an oral treatment for peptic and stress ulcers in adults.[15–17] The successful use of this drug in children with peptic ulcer[18,19] or for prevention of stress ulcer after paediatric cardiac surgery has been reported.[20] Pirenzepine i.v. before surgery in adults has been shown to reduce gastric secretion before anaesthesia.[21,22] However, there are no data on the efficacy of preoperative pirenzepine in controlling gastric fluid pH and volume in children.

Thus, the first aim of this study was to examine if preoperative oral pirenzepine reduces gastric fluid at induction of anaesthesia in paediatric patients. In adults undergoing surgery, concomitant use of pirenzepine and a H_2 receptor antagonist was superior to pirenzepine alone.[22,23] Therefore, the second aim of this study was to ascertain if a combination of pirenzepine and a H_2-receptor antagonist is more effective than each drug given alone in paediatric anaesthesia. We used ranitidine at a dose thought to be acceptable in children.[6,24]

Patients and methods

The study comprised two parts. Both were approved by the local Ethics Committee and parental informed consent was obtained for all children.

PATIENTS AND GROUP ASSIGNMENT

In part I, we examined the effects of pirenzepine on gastric fluid pH and volume in 90 healthy, ASA I children, aged 3–14 yr, undergoing elective (ophthalmological, otological, orthopaedic or urological) surgery. Patients with gastrointestinal disease, obese children who were more than 20% heavier than their ideal body weight and those receiving medications known to affect gastric fluid composition or gastric emptying were excluded. The children were allocated randomly to receive one of three medications ($n = 30$ in each group): placebo (group P_0), pirenzepine (Gastrozepin, Boehringer Ingelheim Japan, Kawanishi, Japan) 12.5 mg (group $P_{12.5}$) and pirenzepine 25 mg (group P_{25}). These medications were administered orally 60 min before induction of anaesthesia.

After confirmation of the effectiveness of pirenzepine 25 mg in reducing the number of children thought to be at risk of aspiration pneumonitis in part I of the study, we conducted part II to compare

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Table 1 Patient characteristics (mean (SD) or range)). Group P_0=Placebo; group $P_{12.5}$=pirenzepine 12.5 mg; group P_{25}=pirenzepine 25 mg; group C=placebo and placebo; group P=pirenzepine 25 mg and placebo; group R=ranitidine 75 mg and placebo; group P-R=pirenzepine 25 mg and ranitidine 75 mg. These medications were given orally 60 min before anaesthesia. No significant differences between groups

	Part I			Part II			
	Group P_0	Group $P_{12.5}$	Group P_{25}	Group C	Group P	Group R	Group P-R
n	30	30	30	30	30	30	30
Age (yr)	7.5 (5–14)	7.1 (3–12)	6.8 (3–12)	6.9 (2–11)	7.6 (6–14)	7.2 (3–12)	7.7 (4–14)
Weight (kg)	28 (4.0)	28 (4.1)	25 (3.7)	27 (3.8)	30 (4.1)	29 (4.2)	30 (4.2)
Clear fluids ingested							
Type (tea/water/apple juice)	12/16/2	15/14/1	16/12/2	13/17/0	15/14/1	14/13/3	17/11/2
Volume (ml kg^{-1})	6.3 (2.0)	6.2 (2.1)	6.8 (2.1)	6.4 (2.2)	6.2 (2.1)	6.6 (2.4)	6.8 (2.3)

the efficacy of pirenzepine, ranitidine and the combination pirenzepine–ranitidine in 120 children (2–14 yr). Inclusion and exclusion criteria were identical to those in part I. Patients were allocated randomly to one of four treatments (n = 30 in each group): placebo and placebo (group C), pirenzepine 25 mg and placebo (group P), ranitidine (Zantac, Glaxo-Sankyo, Tokyo, Japan) 75 mg and placebo (group R), and pirenzepine 25 mg and ranitidine 75 mg (group P-R). These medications were also given orally 60 min before induction of anaesthesia.

COLLECTION AND ANALYSIS OF GASTRIC FLUID

All children were prohibited from eating solid food or drinking milk products after 21:00 on the day before surgery, and were instructed to ingest a moderate volume (6–7 ml kg^{-1}) of clear fluid (tea, water or apple juice) until 3 h before anaesthesia. After preoxygenation with 100% oxygen by mask, anaesthesia was induced with nitrous oxide 4 litre min^{-1}, oxygen 2 litre min^{-1} and sevoflurane in gradually increasing concentrations up to 5%. Infusion of lactated Ringer's solution was started immediately after loss of consciousness. Atropine 0.01 mg kg^{-1} i.v. was administered through a three-way stopcock. The lungs were ventilated taking care to avoid inflation of the stomach. Tracheal intubation was facilitated by vecuronium 0.1 mg kg^{-1} i.v. All inductions were uneventful and there was no coughing, laryngospasm or vomiting during induction.

After tracheal intubation, a16-French gauge Argyle Salem Sump catheter was inserted into the stomach. Placement of the orogastric tube within the stomach was verified by auscultation over the epigastrium during introduction of 5–10 ml of air. Gastric fluid samples were obtained by gentle aspiration with a 50-ml syringe by an investigator who was unaware of the premedications given. Pressure was applied over the epigastrium with the patient supine and then in the left and right lateral decubitus positions to ensure maximum emptying of gastric fluid. Gastric contents were inspected visually for particles, and the volume of gastric contents was measured with the syringe. The pH of the gastric fluid was measured immediately using a pH meter (Horiba F-8L, Japan) which was calibrated using standard buffers at pH values of 1, 4 and 7. The pH meter has a precision of 0.01 pH units over the entire pH range. Age, weight, type and volume of clear fluid ingested, and gastric fluid pH and volume were recorded for each patient.

STATISTICAL ANALYSIS

Comparison of data between groups was made using one-way analysis of variance and Bonferroni correction for multiple comparisons of parametric data, while the Kruskal–Wallis rank test was used for non-parametric data. Differences between risk factors for the pulmonary acid aspiration syndrome were tested for significance using the chi-square test. $P < 0.05$ was regarded as statistically significant. Thirty patients in each group were sufficient to detect a difference of 0.7 between groups in gastric volume and pH at a significance level of 0.05 (=α), with a power of 0.85.[25]

Results

There were no differences between the seven groups in age, weight or type or volume of clear fluids ingested (table 1). Although gastric fluid was obtained from all children, the volume was sufficient for pH determination in 77 of the 90 samples and in 97 of the 120 samples in parts I and II, respectively. In the remainder, a very small quantity of gastric fluid remained in the gastric tube and could not be aspirated into the syringe. Such an insufficient quantity of gastric aspirate precluded measurements; these small quantities of gastric fluid were arbitrarily regarded as a residual volume of 0 ml. None of the children had particulate matter in the gastric aspirates. Adverse side effects (eruption, headache, diarrhoea or fever) related to pirenzepine or ranitidine were not observed before surgery.

PART I

As shown in figure 1, gastric fluid volume was less with pirenzepine 25 mg. The lower dose of pirenzepine failed to affect fluid volume significantly. Pirenzepine failed to decrease gastric fluid acidity significantly, regardless of dose. However, pirenzepine 25 mg significantly reduced the proportion of children considered at risk.

PART II

Pirenzepine alone and the combination pirenzepine–ranitidine significantly decreased gastric fluid volume but ranitidine alone did not. In contrast, ranitidine alone and pirenzepine–ranitidine increased significantly gastric fluid pH whereas pirenzepine alone did

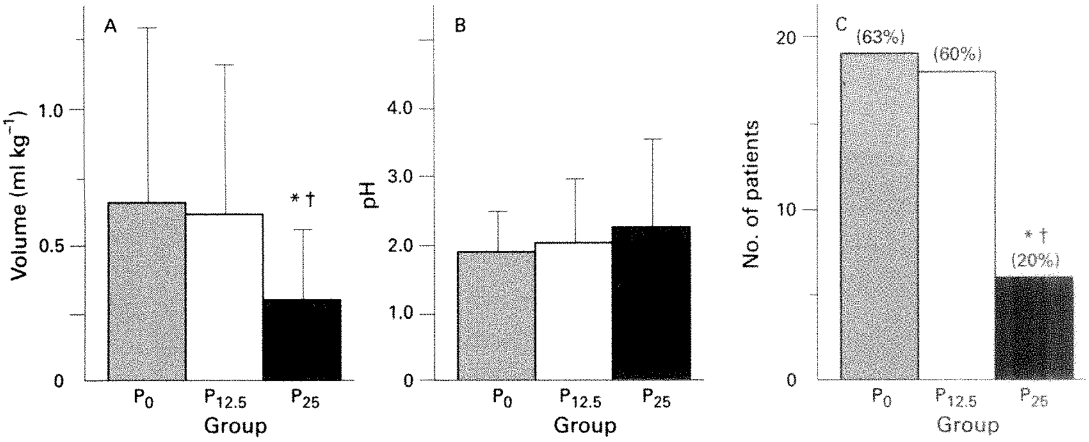

Figure 1 Gastric fluid analysis in part I of the study. Gastric fluid volume (A) and pH (B) are expressed as mean (SD). The percentage of children considered to be at risk of aspiration pneumonitis (C) (volume >0.4 ml kg^{-1} and pH <2.5) is shown in parentheses above each column. Group P_0 = placebo, group $P_{12.5}$ = pirenzepine 12.5 mg, group P_{25} = pirenzepine 25 mg. $^*P < 0.05$ compared with group P_0; $^\dagger P < 0.05$ compared with group $P_{12.5}$.

not. Gastric fluid volume and acidity in the pirenzepine–ranitidine combination group (group P-R) were significantly less than in all other groups (fig. 2). Ranitidine alone and pirenzepine alone reduced the proportion of children with a gastric fluid pH <2.5 and gastric fluid volume >0.4 ml kg^{-1}. Concomitant use of pirenzepine and ranitidine reduced the number of children deemed at risk to zero.

Discussion

Gastric secretion is regulated by nervous and hormonal mechanisms.[26] Nervous regulations act through the parasympathetic fibres of the vagus nerves, and hormonal regulation takes place mainly in response to gastrin. Receptors for histamine, acetylcholine and gastrin, all of which are stimulants for secretion of gastric acid, have been identified on the parietal cells in the gastric glands.[26]

Muscarinic cholinergic receptors are classified pharmacologically into three subtypes (M1, M2 and M3).[14] M1 receptors are found in ganglia and various secretory glands, M2 receptors predominate in the myocardium and also appear to be found in smooth muscle, and M3 receptors are located in smooth muscle and secretory glands. Pirenzepine has a high affinity for M1 receptors with low affinity for M3 receptors.[14, 15] The drug is thought to inhibit secretion of gastric juice mainly by blocking binding of acetylcholine to M1 or M3 receptors, although the precise mechanism is unknown. Although pirenzepine also combines with M1 receptor on the ganglia of the vagus nerve, the nerve-mediated mechanism probably has less involvement in the anti-secretory action compared with antagonism of the gastric gland itself. The specificity for the muscarinic receptors contributes to the advantages of pirenzepine, with little effect on the heart (tachycardia), eye (mydriasis), bladder (disturbed urination) or gut (constipation).[14, 27] Although the M1 subtype is found in the central nervous system (CNS), central effects of pirenzepine are not seen because of its low lipid solubility and limited penetration into the CNS.[15] The drug also inhibits secretion of gastrin, unlike omeprazole or H_2 receptor antagonists.[28] Pirenzepine has been shown to reinforce protective factors against gastric ulcer by increasing the blood flow of the gastric mucous membrane[29] and inhibiting reduction of gastric mucus production.[30] These characteristics may also give the drug additional advantages.

The rationale for the timing and doses of pirenzepine in our study were based on data from others. Onset of the gastric anti-secretory effect of pirenzepine occurs within 60 min after a single oral dose.[31] Pirenzepine has an accepted place in clinical practice for the treatment of severe gastritis and peptic ulcer in adults. For this purpose, pirenzepine 50–150 mg day^{-1} (1–2 mg kg^{-1} day^{-1}) given orally for several weeks of months is advocated.[16, 17] A single i.v. injection of pirenzepine 10 mg to adults has been used to prevent postoperative stress ulcer and is effective in reducing the number of patients at increased risk of the acid aspiration syndrome.[21, 22] The dose used in this study (12.5–25 mg) may be inappropriate in children because of morphological and pharmacokinetic factors. Pirenzepine 25–100 mg day^{-1} has been used in the treatment of gastric duodenal ulcer in children.[18] For control of long-term gastric pH after gastroduodenal ulcer haemorrhage in three children, pirenzepine 0.5–1 mg kg^{-1} day^{-1} was used.[19] No major adverse effects were observed. Although use of pirenzepine 50 mg may have been more effective, this large dose was not chosen to ensure safety in the initial evaluation of the effects of pirenzepine in this setting.

Reports on the effects of preoperative pirenzepine on gastric fluid in adults have been published. In all of these studies, premedication with i.v. pirenzepine successfully decreased gastric fluid volume.[21, 22] However, the effects on gastric fluid pH are conflicting. In several studies, pirenzepine failed to increase pH.[32, 33] Addition of other drugs (e.g. atropine or H_2 antagonists) to pirenzepine has been used successfully in adults to combat this drawback of pirenzepine.[21, 22] In this study, we observed phenomena similar to those in adult studies.

The efficacy of preoperative H_2 antagonists as acid aspiration prophylaxis has been demonstrated in children.[5, 6, 8-11] However, the reduction in gastric fluid volume is not a consistent finding in studies of H_2 antagonists, including ranitidine.[8-11] In our study, children who received ranitidine had gastric fluid volumes similar to those in the control group. The inability of H_2 antagonists to decrease gastric volume

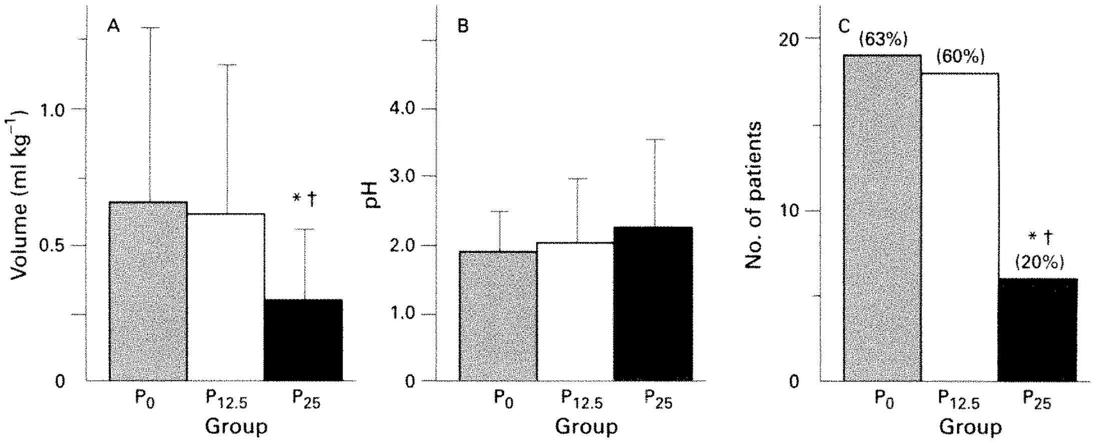

Figure 2 Gastric fluid analysis in part II of the study. Gastric fluid volume (A) and pH (B) are expressed as mean (SD). The percentage of children considered to be at risk of aspiration pneumonitis (C) (volume >0.4 ml kg^{-1} and pH <2.5) is shown in parentheses above each column. Group C = placebo and placebo, group P = pirenzepine 25 mg and placebo, group R = ranitidine 75 mg and placebo and group P-R = pirenzepine 25 mg and ranitidine 75 mg. $*P < 0.05$ compared with group C; $\dagger P < 0.05$ compared with group R; $\ddagger P < 0.05$ compared with group P.

may be a disadvantage compared with pirenzepine. However, because the risk of aspiration depends to a greater degree on gastric fluid pH, which is invariably increased by H_2 antagonists, than on volume, H_2 antagonists may be more suitable for prophylaxis than pirenzepine. In this study, we have shown that the pirenzepine–ranitidine combination reduced both gastric fluid volume and acidity, suggesting a potential use for this combination in clinical practice. However, these findings do not lead us to advocate this approach instead of rapid sequence induction in children at risk of aspiration pneumonitis.

In summary, we have shown that oral preoperative pirenzepine 25 mg (but not 12.5 mg) reduced gastric fluid volume in children but was ineffective in increasing gastric fluid pH to >2.5. In contrast, ranitidine 75 mg increased pH but failed to decrease volume. The combination of pirenzepine and ranitidine was superior to each drug alone for improvement in gastric fluid environment. In children who are at risk of aspirating gastric contents, the reduction in gastric fluid volume and acidity by this combined prophylactic intervention can reasonably be anticipated to provide protection against the occurrence of pneumonitis, should regurgitation and aspiration of gastric contents occur.

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British Journal of Anaesthesia 1998; **80**: 58–62

LABORATORY INVESTIGATIONS

Errors on anaesthetic record charts as a measure of anaesthetic performance during simulated critical incidents

A. J. BYRNE, A. J. SELLEN AND J. G. JONES

Summary

We have measured the performance of 10 trainee anaesthetists during a single simulated anaesthetic during which there was a complex critical incident. Errors in the recording on the anaesthetic charts of the "patient's" oxygen saturation, heart rate, systolic and diastolic arterial pressures and end-tidal carbon dioxide concentrations were used as a measure of mental workload and hence performance. The critical incident was designed to be stressful and contained, in sequence, episodes of hypotension, arrhythmia and bronchospasm. Chart recording errors increased markedly during the critical incident ($P < 0.01$) and decreased subsequently when the "patient" had stabilized. More than 22% of the values charted during the simulation were in error by more than 25% of the real value, and errors in excess of 100% of the actual value were recorded. There was no evidence of a tendency to consistently underestimate the magnitude of abnormal values. This method is appropriate for assessing the performance of groups of anaesthetists during simulated critical incidents. It also raises questions on the accuracy of anaesthetic record charts when recording critical incidents. (*Br. J. Anaesth.* 1998; **80**: 58–62)

Keywords: anaesthesia, audit; model, computer simulation; computers, simulation; anaesthetist, performance

"Mental workload" is a term often used to describe the amount of mental effort involved in performing any given task.[1] If we consider that there is a limit to the rate at which information can be processed by the human mind ("mental capacity"), then a simple model of mental workload is that it is a function of the proportion of this capacity in use at any time. The proportion of capacity in use varies depending on the difficulty or demands of the task. It is also generally accepted that as we acquire experience of a new task and develop procedural skills, the mental workload associated with that task decreases, because our capacity increases. For example, learner drivers need all their abilities just to keep the car on the road, while taxi drivers are able, with ease, to drive, eat, navigate and talk simultaneously. Studies in fields such as aviation have shown that high mental workload is associated with poor performance. Casali and Weirwille[2] noted that, "If requirements are moderately excessive, there may be a measurable degradation in the performance of simple, supportive tasks associated with flying, such as routine communications or engine instrument monitoring. Often, more immediate tasks receive the focus of attention, and other tasks are time shared or even ignored completely. Mental overload may further result in significant pilot errors in aircraft control, possibly culminating in an accident". The inference from these two observations is that a low mental workload during the performance of a complex task may be associated with expertise while a high mental workload for the same task may be associated with inexperience and loss of control. If the mental workload of a subject performing a standardized task can be measured, then it can provide an assessment of performance.

Several techniques have been used to measure mental workload, many relying on the use of a secondary task.[3] In such studies, the subject is asked to perform two tasks, a primary task (which is regarded as essential) and a secondary task (which has a lower priority). In this situation, the mental capacity of the subject must be shared between the two tasks. If a subject performs the primary task well, their mental workload is low, allowing spare capacity to be allocated to the secondary task. Conversely, if the subject performs the primary task badly, their mental workload is high and there is little spare capacity available for the secondary task. Thus performance on the secondary task can be used as an indication of how much spare capacity is available and is therefore a measure of the subject's performance in the primary task.

The problem with this type of research in anaesthesia is the difficulty in finding a secondary task which subjects repeat frequently enough to obtain good measures of performance, but which does not distort performance of the primary task (i.e. does not interfere with normal working patterns). The most common methods used in other fields have involved choice reaction time, memory, monitoring and tracking tasks.[3] In anaesthesia, Gaba and Lee[4] studied the workload of anaesthetists during real anaesthetic cases by asking them to add together two numbers on the screen of a computer every 45 s. They were asked to observe when the numbers

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changed and enter their answer into the computer via the keyboard. The study showed that in times of stress, the anaesthetists took longer to add the numbers or failed to respond at all. Unfortunately, the addition of a monitor and a keyboard to an already complex theatre in addition to the risk of distracting the anaesthetist from their patient makes the technique unsuitable for routine use in real theatres. Further, the use of such techniques detracts from the realism of simulated events.

Our purpose in this study was to examine a secondary task technique, completion of the anaesthetic record chart, which can be more realistically incorporated into the simulation of an anaesthetic critical incident. This also has the potential of being used during anaesthetics involving real patients. During previous studies with the ACCESS[5 6] simulator we noticed that anaesthetists' perceptions of events during simulated anaesthetics were often very distorted.[7] In particular, when anaesthetists were asked to complete an anaesthetic chart after the simulation had finished, the charted values showed large errors and the time scale was overestimated by up to 100%. The errors we observed were similar to those detected during other studies involving measurement of mental workload.[3] It was therefore decided to investigate if chart error could be used as a measure of mental workload and hence performance.

Methods

Ten trainee anaesthetists completed a single simulation of an anaesthetic using the anaesthetic computer-controlled emergency situation simulator (ACCESS), a full scale, low-cost anaesthesia training simulator.[5] Each anaesthetist was introduced to the simulation as if taking over a routine case from a colleague. The "patient" was described as a 25-yr-old female undergoing an anterior cruciate ligament repair under general anaesthesia. She was said to be asthmatic and to be recovering from an episode of viral myocarditis. When the simulation was started, the anaesthetist was asked to behave as if it were a real case, including keeping an accurate, contemporaneous anaesthetic record, but they were not made aware of the purpose of the study. Two changes were made from previous simulations to aid the collection of data. First, the anaesthetic chart had a time scale marked at 2.5-min intervals rather than the usual 5 min to increase the number of data points. This increased the workload of those studied (as does any secondary task method), but we considered that it would not have significantly altered the result because completion of the anaesthetic chart is such a routine part of patient care during anaesthesia.[2] Second, the "patient" and monitors were set to continue through a series of abnormalities irrespective of any of the anaesthetists' actions. This ensured that all anaesthetists were exposed to exactly the same information from the simulator over the same time scale and that task demands would be held constant from simulation to simulation. The simulation lasted 25 min and started with 5 min of normal baseline readings. Hypotension then developed over the next 5 min with systolic arterial pressure decreasing from 90 to less than 60 mm Hg. A supraventricular tachycardia (SVT) of 160 beat min^{-1} then started and arterial pressure increased to normal. Five minutes later the SVT terminated and at the same time bronchospasm developed. After another 5 min, the bronchospasm reduced and the simulation ended with 5 min of "normality". Although the scenario seemed rather contrived, we have noticed during previous studies that those being tested become so involved in treating their "patient", that the behaviour of the simulator was rarely questioned. We expected therefore that the anaesthetists would treat each abnormality as it arose, as if it were a real case.

Table 1 Median errors for all 10 anaesthetists at the first time point

Variable	Median error
Heart rate	0.9 beat min^{-1}
Systolic/arterial pressure	5.4 mm Hg
Diastolic/arterial pressure	3 mm Hg
Oxygen saturation	0.3%
End-tidal carbon dioxide	0.08 kPa

At the end of the simulation each anaesthetist was allowed to enter any omitted data on their anaesthetic chart. A print-out of the values shown on the simulator's monitor was then obtained from the computer. The charted values of heart rate, systolic arterial pressure, diastolic arterial pressure, oxygen saturation and end-tidal carbon dioxide values obtained from the anaesthetic chart and the real values from the simulator print-out were compared and the difference between each of the paired (charted and real) values was calculated. To standardize the error for each variable, the median error for each of the variables was then calculated for all 10 anaesthetists at the first (2.5 min) time. These values are shown in table 1 and were taken to represent the performance of the anaesthetists in the unstressed, baseline state. All subsequent errors were divided by the baseline value to provide a standardized error. An error greater than 1 therefore represents a performance worse than baseline and less than 1 better than baseline. At each time the median standardized error, range and interquartile range for all 10 anaesthetists was calculated.

If a reading was missing from the anaesthetic chart it was allocated the same percentage error as the other readings at that time. If, at a particular time, none of the five variables was charted, it was assumed that the readings were unchanged from the previous entry and the error calculated accordingly.

To analyse the way in which anaesthetists were using each of the monitors, the data for each monitor were separated and the median standardized error for all 10 anaesthetists was calculated at each time. For statistical analysis, data for all variables for the first time were taken to represent the baseline, unstressed state. The median standardized error and interquartile range were then calculated. Data from the other times were classified into one of the four quartile ranges of the first time. This method was chosen because the data were positively skewed and so unsuitable for parametric analysis. A chi-square analysis was carried out, with $P < 0.05$ taken as significant. Manipulation of the data and drawing of the graphs were carried out using a standard spreadsheet (EXEL, Microsoft Corporation).

Table 2 An example of the data from a simulation completed by a single anaesthetist (see text for details of calculations)

	Time (min)									
	2.5	5	7.5	10	12.5	15	17.5	20	22.5	25
Real		Hypotension			Arrhythmia		Bronchospasm			
Heart rate	72	73	74	160	160	90	90	72	72	72
Systolic	97	87	60	97	97	65	65	96	97	97
Diastolic	52	47	32	52	52	35	35	51	52	52
Sa_{O_2}	99	97	96	92	92	86	86	98	98	98
PE'_{CO_2}	4.5	5.4	4.2	2.6	2.5	5.2	5.4	4.5	5.2	5.2
Charted										
Heart rate	72	72	75	73	160	160	160	143	76	72
Systolic	98	98	88	55	93	93	94	63	64	92
Diastolic	53	52	48	48	48	48	48	48	48	48
Sa_{O_2}	99	99	97	97	95	88	86	86	87	98
PE'_{CO_2}	4.4	4.5	5.4	5.4	2.8	2.4	2.5	2.9	2.9	4.4
Standardized error										
Heart rate	0	1	1	96	0	78	78	79	4	0
Systolic	0	2	5	8	1	5	5	6	6	1
Diastolic	0	2	5	1	1	4	4	1	1	1
Sa_{O_2}	0	7	3	17	10	7	0	40	37	0
PE'_{CO_2}	1	11	15	35	4	35	36	20	29	10
Median standardized error	1	2	5	17	1	7	5	20	6	1

Results

All anaesthetists treated their "patient" in an appropriate manner and successfully completed the simulation. All anaesthetists eventually used a sympathomimetic drug to treat the hypotension. This treatment was then blamed for the production of the supraventricular tachycardia. Arrhythmia usually prompted discontinuation of the volatile anaesthetic and the resulting reduction in depth of anaesthesia was blamed for the bronchospasm. The final phase of normality was accepted as evidence of the success of the anaesthetist's treatment with either aminophylline, epinephrine or salbutamol.

Data from a single anaesthetist are shown in table 2. Data for all five variables were available from both the anaesthetic charts and the simulator in all cases. The real values shown on the monitors are at the top and the values charted by the anaesthetist are shown below. Calculations were performed as described in the methods section. For clarity all calculated values are shown as integers. Actual calculations were performed using a spreadsheet and the output imported directly into graph drawing software to produce the figures.

Figure 1 shows the median standardized error, interquartile range and range for the five variables, recorded by all 10 anaesthetists. There was a clear increase in median charting error with the onset of the critical incident and a subsequent decrease, although the range was wide. Compared with the results in the first time period, all subsequent results were significantly worse ($P < 0.01$).

Figure 2 shows the median standardized error for three of the variables, as charted by all 10 anaesthetists over the period of the simulation. The data for systolic and diastolic arterial pressures were intermediate and have been omitted for clarity. There was a wide variation in error, but interestingly, the error in charting heart rate was lower than that of end-tidal carbon dioxide during the normal, hypotension and arrhythmia phases. In contrast, during the episode of bronchospasm (from 15 to 20 min), the error in heart rate charting increased above that of end-tidal carbon dioxide.

Discussion

We have shown that it is possible to use error in anaesthetic chart recording as a measure of mental workload and hence performance. Importantly, the method is not intrusive and is less likely to interfere with the normal activities of anaesthetists than methods of measuring mental workload described previously. Our method avoids the inter-observer variability which caused problems with a rating scale tested previously by another group.[8] It also does not require the use of videotaping, which is expensive and time consuming to analyse.

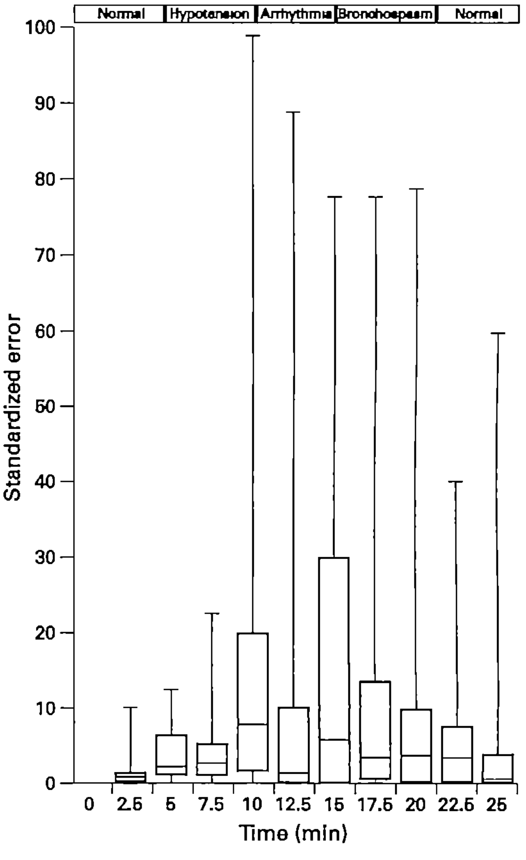

Figure 1 Median standardized error for all 10 anaesthetists during the period of the simulation (interquartile range, range).

This study may be criticized for not involving real anaesthetized patients and for not taking into account the many reasons why those studied may have chosen not to fill in the chart accurately. However, the secondary task method has been used in some industries for many years and has been shown to identify subjects who were subsequently successful in their jobs.[3] It has been suggested that one of the causes of error is the, possibly subconscious, reluctance of anaesthetists to chart abnormal values to avoid later criticism. However, examination of table 1 shows that where the error was greater than 10%, 11 of the charted values erred on the side of normality while 12 were more abnormal than the real values. This supports the view that errors are not introduced deliberately by the anaesthetist, but are caused by excessive mental workload. Another problem is that even with standardization, the variables studied have different normal ranges and variability so that, for example, an error in oxygen saturation of 10% may be considered to be much more significant than a similar error in systolic pressure, making comparisons between variables difficult. It is true that the errors for each of the variables studied are not directly comparable and simply standardizing the values results in loss of information. We suggest that interpretation of the results always requires a detailed knowledge of the circumstances under which the data were collected and of the psychological theory on which this method is based. However, our method has the advantage of producing a clear and easily comprehended result and the error of each variable can easily be studied individually if further information is needed.

The results in figure 1 show that chart error was clearly related temporally to the critical incident. This association was highly significant, even in this small study. However, the wide variability in error indicates that to provide a valid assessment of an individual, their performance over a range of tasks needs to be studied.

Figure 2 shows that the error was not divided equally between different monitored variables. Other research has indicated that, as situations become more complex and stressful, subjects tend to shed tasks and information so as to concentrate on what is perceived as important. It is interesting that the error in charting heart rate was generally low and then increased markedly during the period of bronchospasm, much more than that of end-tidal carbon dioxide. The inference is that the anaesthetists usually attended to the heart rate, but during a respiratory problem their attention was shifted elsewhere. This is perhaps unsurprising but almost impossible to quantify with any other method. The observation that charting error changes with the task suggests that it may be possible to assess new ways of presenting information during anaesthesia and allows the evaluation of new monitors without putting patients at risk.

As our previous study[7] indicated, our perception of events can differ widely from reality. While this study was designed to remove the previously demonstrated distortion of time associated with increased workload, we were still able to demonstrate an increase in chart recording error with the onset of a simulated critical incident. This is a strong indication that mental overload had occurred or was imminent in those tested. Solutions to such a problem are not clear at present. Techniques such as analysis of charting error may allow us to evaluate a variety of possible solutions in a scientific way. Thus if training and changes to equipment or the theatre environment lead to reduced mental workload, then it is likely that the chances of future errors is also reduced.

We must stress that the use of chart error is not necessarily appropriate for use in assessing the performance of individual anaesthetists, in real operating theatres, by retrospective analysis of their anaesthetic charts. First, the operating room is a complex environment and the care of the patient involves a variety of tasks, any one of which may rightly take precedence over completion of the anaesthetic chart. Second, the limitations of the monitors in current use may mean that we cannot always accept their output as a true reflection of the condition of the patient. Third, performance is not synonymous with competence. Poor performance cannot be equated with standards of patient care. However, this method might be applied to real anaesthetics, not for assessing individuals, but rather for assessing performance of groups of anaesthetists. For example it might be used to compare the results from a large group of anaesthetists across theatres, to assess the impact of equipment configurations or theatre layouts.

This study has another important implication. At present, the accuracy of the anaesthetic chart is important in the legal definition of acceptable standards of patient care. This study indicates that in a real critical incident, the accuracy of any anaesthetic chart is highly questionable. Further, the more stressful the situation, the less likely the chart is to be accurate. Thus the relevance of anaesthetic chart accuracy to the legal process must be questioned.

Finally, a recent editorial[9] commented that the increasing safety of anaesthesia is progressively reducing the value of studies such as the Confidential Enquiry into Maternal Deaths because deaths caused by anaesthesia have become so uncommon. To continue this progress, we need techniques which

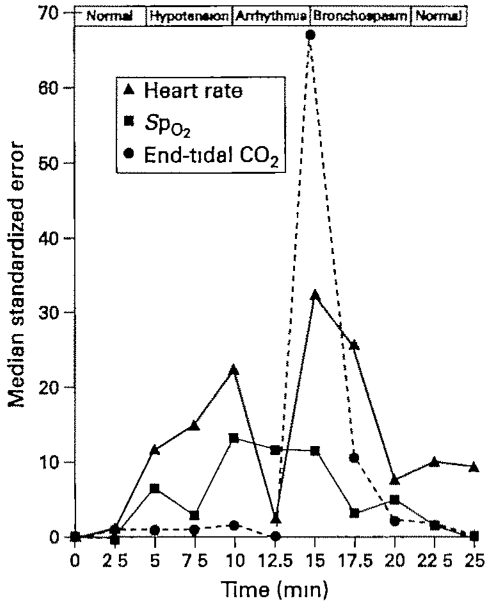

Figure 2 Median standardized error for three variables for all 10 anaesthetists during the period of the simulation. (Values for systolic and diastolic arterial pressures were intermediate and have been omitted for clarity.)

can detect poor performance even when it only has the potential to cause harm to patients. We believe that the use of secondary task techniques and chart error in particular may provide a way of assessing potential safety problems before errors and accidents occur.

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Interactive effect of morphine and dexmedetomidine on gastric emptying and gastrointestinal transit in the rat†

T. Asai, W. W. Mapleson and I. Power

Summary

We studied the interactive effect of dexmedetomidine and morphine on gastric emptying and gastrointestinal transit in the rat. In one group of rats, to examine the interactive effect on gastrointestinal transit, the two drugs were injected i.p. in a fixed ratio (30: 1)—that of their ED_{50} values—in six doses (0.062–1.075 mg kg^{-1}), each to a different group of 5–8 male rats for each dose. In another group, to examine the interactive effect on gastric emptying, either dexmedetomidine or saline was injected with saline or with the ED_{25} or ED_{50} of morphine (0.22 and 2.8 mg kg^{-1}, respectively). In both groups, at 30 min, radiolabelled saline 1 ml was infused into the stomach; at 1 h, gastric emptying or gastrointestinal transit was calculated by measuring the radioactivity in the gastrointestinal tract. Morphine and dexmedetomidine produced a supra-additive inhibitory effect on gastrointestinal transit ($P = 0.02$). Dexmedetomidine 0.01 mg kg^{-1}, which itself significantly inhibited gastric emptying ($P < 0.01$), did not significantly alter the inhibitory effect of morphine on gastric emptying. Therefore, in rats, dexmedetomidine markedly enhanced the inhibitory effect of morphine on gastrointestinal transit, but it did not significantly alter the effect on gastric emptying. (*Br. J. Anaesth.* 1998; **80**: 63–67)

Keywords: gastrointestinal tract, emptying; interactions (drug), morphine; interactions (drug), dexmedetomidine; sympathetic nervous system, dexmedetomidine; rat

Opioids are used widely as powerful analgesics but they produce several side effects.[1] Alpha$_2$ adrenoceptor agonists reduce anxiety, induce sedation and analgesia, while producing less respiratory depression, nausea, vomiting and pruritus than opioids.[2 3] However, the use of alpha$_2$ adrenoceptor agonists may be limited because of their depressant effects on arterial pressure and heart rate.[4 5] Concurrent injection of drugs of different categories—such as an opioid and an alpha$_2$ adrenoceptor agonist—may reduce the required dose of both drugs, and thus may reduce the severity of complications associated with each drug. In addition, there has been considerable evidence that concurrent administration of a mu opioid receptor agonist and an alpha$_2$ adrenoceptor agonist produces supra-additive analgesia[6 7] and sedation.[8] In addition, there is some evidence for lack of enhanced respiration.[9–11]

In earlier experiments, we found that morphine strongly inhibited both gastric emptying and gastrointestinal transit to a similar degree, whereas the alpha$_2$ agonists, clonidine and dexmedetomidine, only weakly inhibited gastric emptying despite their marked inhibitory effect on intestinal transit.[12] Therefore, it is possible that concurrent injection of morphine and an alpha$_2$ agonist would produce marked inhibition of intestinal transit with relatively weak inhibition of gastric emptying. The interactive effects of a mu opioid receptor agonist and an alpha$_2$ adrenoceptor agonist on gastric emptying are not known.

The aim of this study was to examine the interactive effect of morphine and dexmedetomidine on gastric emptying and gastrointestinal transit of liquids in the rat.

Materials and methods

The study was conducted under the Animal (Scientific Procedures) Act 1986 (Home Office Licence: PPL 40/1397). Male Wistar rats, weighing 200–250 g, were housed under standard controlled environmental conditions, with a 12 h light–dark cycle. The animals were fasted for 24 h, but they were allowed free access to water until 20–30 min before the start of the experiment. Each animal was kept individually in a wire-mesh cage to prevent coprophagy during fasting. All experiments were started between 10:00 and 11:00. Dexmedetomidine (Orion-Famos Pharmaceuticals, Finland) and morphine (Sigma Chemical Co. U.K.) were prepared freshly on each day of the experiment.

A group of six rats was allocated for each study. If more than one rat was excluded, another group of six rats was used until a group was completed in which no more than one rat was excluded. Data from the non-excluded rats from all groups for each study (5–8 rats) were used.

Gastric emptying and gastrointestinal transit were studied separately in different groups of rats.

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GASTROINTESTINAL TRANSIT

In one set of six groups of rats, the interactive effect of morphine and dexmedetomidine on gastrointestinal transit was studied. The two drugs were always injected in a fixed ratio (30:1)—that of their ED_{50} values obtained in earlier experiments (morphine 1.2 mg kg^{-1}; dexmedetomidine 0.04 mg kg^{-1}).[12] We used six different doses (0.062–1.075 mg kg^{-1}) which included the ED_{50} predictable on the basis of additivity.

GASTRIC EMPTYING

The inhibitory effect of dexmedetomidine on gastric emptying is weak.[12] Therefore, the interactive effect of morphine and dexmedetomidine on gastric emptying was studied in a separate set of six groups of rats. Three pairs of groups of rats received the following six combinations of drugs: pair 1:(1) saline and saline; (2) saline and dexmedetomidine 0.01 mg kg^{-1}; pair 2:(1) morphine 0.22 mg kg^{-1} (ED_{25}) and saline; (2) morphine 0.22 mg kg^{-1} and dexmedetomidine 0.01 mg kg^{-1}; pair 3:(1) morphine 2.8 mg kg^{-1} (ED_{50}) and saline; and (2) morphine 2.8 mg kg^{-1} and dexmedetomidine 0.01 mg kg^{-1}.

Gastric emptying and gastrointestinal transit were studied, as described previously.[12] In brief, at 0 min, a substance or a combination of substances (see below), in a volume of 1.0 ml kg^{-1} for each rat was given i.p. At 30 min, 1.0 ml of saline containing radiolabelled sodium chromate was infused into the stomach. At 60 min, the rats were killed, the stomach and small intestine removed, and the small intestine divided into 10 equal segments. Radioactivity in the stomach and each segment of the intestine was measured. If there was chyme in either the stomach or small intestine, the data were not used.

Gastric emptying and gastrointestinal transit (expressed in terms of the geometric centre) in each rat and percentage inhibition of gastric emptying or gastrointestinal transit for each drug were calculated.[12]

STATISTICAL ANALYSIS

Gastric emptying

The Mann-Whitney *U* test was used to test the effect of dexmedetomidine compared with saline on gastric emptying: on its own, in the presence of the ED_{25} dose of morphine and in the presence of the ED_{50} dose of morphine. Confidence intervals were calculated for median differences, between groups, for gastric emptying. $P < 0.05$ was considered significant.

Gastrointestinal transit

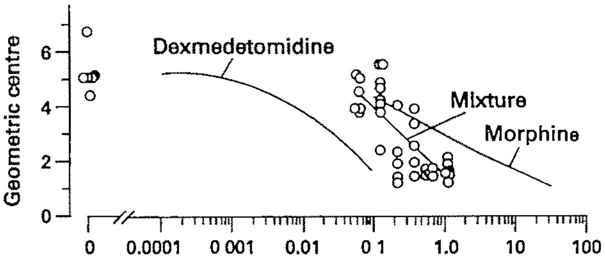

Figure 1 Effect of a mixture of morphine and dexmedetomidine on gastrointestinal transit of saline: values obtained from each rat (open circles), with fitted logit dose–response curves for the mixture and for each drug individually (the latter reproduced from Asai, Mapleson and Power[12]). The equation for percentage inhibition is $y = e^z/(1 + e^z)$, where $z = 1.011 + 2.226 \times \log x$ and x = dose of the test drug. The two drugs were always injected at a fixed ratio (30:1)—that of their ED_{50} values obtained in earlier experiments (morphine 1.2 mg kg^{-1}; dexmedetomidine 0.04 mg kg^{-1}).[12] Symbols were slightly displaced if there were similar values for any given dose. The values at zero dose are for the saline control.

The dose–response curve (variation of percentage inhibition with dose) of the 30:1 mixture of morphine and dexmedetomidine was modelled by fitting a sigmoid logit curve to fractional inhibition against log dose.[12] This was performed using the statistical package GLIM (generalized linear interactive modelling).[13 14] The output provided the information required to calculate the ED_{50} of the mixture, and hence the contribution from each component to that dose: 30/31 and 1/31 of the ED_{50} of the mixture for morphine and dexmedetomidine, respectively. The confidence limits of the ED_{50} of the mixture were obtained using the Fieller equation; the confidence limits of the doses of the two components were taken as 30/31 and 1/31 of those of the mixture. This was justified because the experimental error in making up the 30:1 mixture was negligible in comparison with the uncertainty in the ED_{50} values.

If the two drugs were simply additive, the concentration of each component of our fixed-ratio mixture required for 50% inhibition would be half the ED_{50} of the component on its own. The "theoretical" additive dose is then the sum of these two "half doses". Confidence limits of the components of this theoretical additive dose of the fixed-ratio mixture were determined by an adaptation (see appendix) of the method described by Tallarida, Porreca and Cowan.[15]

Results

GASTROINTESTINAL TRANSIT

Injection of the fixed-ratio mixture of dexmedetomidine and morphine produced a progressive dose-dependent inhibition of gastrointestinal transit (fig. 1).

An isobolograph[15 16] (fig. 2) showed that the required dose (P_1) was below the isobole. Although the confidence intervals for the components of the actual and theoretical additive ED_{50} values of the mixture overlap, the difference between the two ED_{50} values was significant (table 1). Therefore, morphine and dexmedetomidine produced a supra-additive interaction for the inhibitory effect on gastrointestinal transit.

GASTRIC EMPTYING

Dexmedetomidine alone significantly inhibited gastric emptying but when combined with morphine (ED_{25} or ED_{50}) the increase in inhibition was small and not significant.

Discussion

GASTROINTESTINAL TRANSIT

This study showed a clear supra-additive interaction between the effect of morphine and dexmedetomidine on gastrointestinal transit for a 30:1 mixture at the

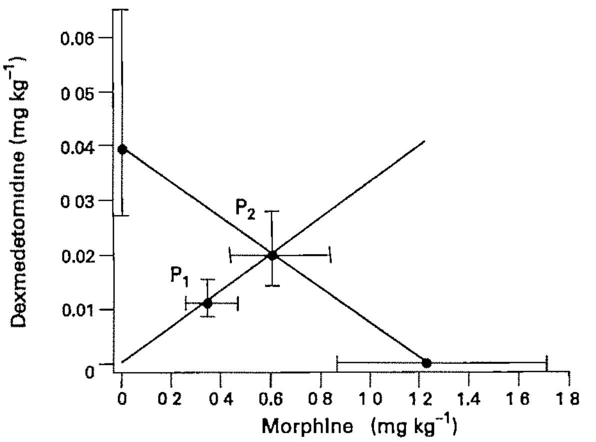

Figure 2 An isobolograph for the interaction of the inhibitory effect of morphine and dexmedetomidine on gastrointestinal transit. The downward sloping line (isobole) connecting the ED_{50} values of each drug separately is the theoretical additive line. The point (P_1) on the isobole is the theoretical additive ED_{50} of the mixture of the drugs (with 95%confidence intervals for each component). The actual ED_{50} of the mixture (P_2) (with 95%confidence intervals) is below the isobole, indicating that there is a supra-additive interaction for the inhibitory effect of these two drugs on gastrointestinal transit; difference in ED_{50} = 0.275, SE difference = 0.114, t = 2.4 (df 34), P = 0.02.

ED_{50} level. Results for mixtures of different ratios, or at other levels of effective dose, might have been different.

Puig, Pol and Warner[17] studied the interactive effect of clonidine and morphine on gastrointestinal transit (but not gastric emptying) in mice using a charcoal meal. They studied three dose levels (ED_{20}, ED_{50} and ED_{80}) for each drug separately, and three mixtures of the two, in the following proportions: "1:1" (equal fractions of the ED_{50} of each), "1:0.33" and "1:3". They found that with the 1:3 and 1:1 mixtures, concurrent injection of these drugs at their ED_{20} or ED_{50} values produced a supra-additive inhibitory effect (an additive interaction was observed with the 1:0.33 mixture). Our results are consistent with those of Puig, Pol and Warner.[17]

Puig, Pol and Warner[17] also claimed that a mixture of clonidine and morphine at higher doses (ED_{60} or ED_{80}) produced sub-additive interactions in inhibiting gastrointestinal transit. However, there are major inconsistencies between their tables and figures.[18] If their figures for ED_{60} and ED_{80} are re-plotted in accordance with the data in their tables, the mixture is (probably not significantly) supra-additive at ED_{60} and not significantly different from additive at ED_{80}.[18] Despite this uncertainty, it seems reasonable to conclude that at lower doses morphine and an alpha$_2$ adrenoceptor agonist (both clonidine and dexmedetomidine) may produce a supra-additive inhibitory effect on gastrointestinal transit. In addition, if higher doses of these drugs cause a sub-additive effect, this may not be clinically relevant.

GASTRIC EMPTYING

Mu receptor selective opioids markedly delay gastric emptying.[12 19] In contrast, alpha$_2$ adrenoceptor agonists have generally been reported to have either no or a weak inhibitory effect on gastric emptying,[12 20–22] although a strong inhibitory effect has been reported in some studies.[23 24] In this study, dexmedetomidine, which itself weakly but significantly delayed gastric emptying, did not significantly alter the inhibitory effect of morphine on gastric emptying.

Table 1 Theoretical additive ED_{50} and actual ED_{50} values, with their variances for the mixture of morphine and dexmedetomidine at a ratio of 30 : 1

	ED_{50} (mg kg^{-1})	Variance	Standard error	t	P
Theoretical	0.625	0.01019	—	—	—
Actual	0.351	0.00277	—	—	—
Difference	0.274	0.01296	0.1138	2.4	0.02

CLINICAL IMPLICATIONS

The incidence of diarrhoea is high (30–40%) in critically ill patients.[25 26] In these patients, gastric emptying is often delayed and consequently may increase the incidence of pulmonary aspiration of gastric contents.[27 28] One method of treatment for diarrhoea is to use drugs which delay intestinal transit and decrease the net secretion of fluid from the intestine. It is desirable to use drugs or combinations of drugs which achieve this without markedly delaying gastric emptying.

Opioids, such as codeine or loperamide, have been used widely as antidiarrhoeal drugs.[29 30] Alpha$_2$ adrenoceptor agonists also inhibit diarrhoea produced artificially by several substances, such as castor oil or prostaglandin E_1.[31 32] They also inhibit diarrhoea in animals with opioid withdrawal symptoms, produced by injecting a series of high doses of opioids and then injecting naloxone.[33 34] In patients, these agonists have been reported to be effective in inhibiting diarrhoea associated with several different diseases.[35 36]

Concurrent administration of an opioid and an alpha$_2$ adrenoceptor agonist produces a supra-additive antinociceptive effect,[6 7] sedation[8] and inhibition of gastrointestinal transit, but not respiratory depression[9-11] or gastric emptying. Therefore, concurrent administration of these drugs may be appropriate as antidiarrhoeal therapy; however, the use of this combination for pain management could be restricted by enhanced sedation and constipation.

In summary, we have shown that, in the rat, dexmedetomidine markedly enhanced the inhibitory effect of morphine on gastrointestinal transit, whereas it did not significantly alter the effect of morphine on gastric emptying.

Appendix

The Fieller equation provides a means of estimating the uncertainty of the ratio of two random, normally distributed variables. The input required includes the variances of the numerator and denominator; the output is in the form of asymmetric confidence limits.

Determination of the confidence limits of the theoretical additive ED_{50} of a mixture of two drugs requires application of the Fieller equation to a ratio in which the uncertainties in the numerator and denominator have been estimated by a previous application of the equation and are therefore in the form of asymmetric confidence limits, not of variances.

The approach described in detail by Tallarida, Porreca and Cowan[15] is to use an approximate form of the Fieller equation to yield a variance (implying symmetrical confidence limits), we adopted a different approach as follows.

When the variance of a parameter estimate is known, 95% confidence limits are calculated from $l_u = x + t_{\nu,0.05} \times$ SE and $l_l = x - t_{\nu,0.05} \times$ SE where l_u and l_l = upper and lower confidence limits, x = parameter estimate, $t_{\nu,0.05}$ = value of Student's t for ν degrees of freedom and $P = 0.05$, and SE = square root of the variance of the estimate. As can be seen, these limits are symmetrical. In addition, they can be rearranged to calculate back to the variance from the estimate and its confidence limits:

$$\mathrm{SE} = (l_u - x)/t_{\nu,0.05} \text{ and } \mathrm{SE} = (x - l_l)/t_{\nu,0.05}$$

Therefore, the variance of x, $V(x)$, the square of SE, is given by

$$V(x) = (l_u - x)(x - l_l)/(t_{\nu,0.05})^2$$

We used this last equation to provide an estimate of the equivalent variance of an input parameter to the Fieller equation when asymmetrical confidence limits of that parameter had been estimated by a previous application of the equation.

The fact that the confidence limits are asymmetrical indicates that the sampling distribution of the various ratios, and therefore of the numerators or denominators that they become, is not normal, as required by the Fieller equation, but skewed—positively skewed in all our examples. Therefore, the confidence limits and variances which we calculate from these initial confidence limits are approximate. However, when we applied our method to an example given by Tallarida, Porreca and Cowan[15] the result was indistinguishable from those indicated in the isobologram they used to display their results, even though those involved t values of only 4–5.

Also, as we showed in a previous study,[12] in the determination of the ED_{50} of a drug, the assumptions about the error distribution are not met in our method (logit curve plus binomial error) and even less so in the conventional method (logit transformation plus normal error). Accordingly, even the basic ED_{50} values, and especially their confidence limits, are approximate. Therefore we resorted to the "bootstrap" technique[37–39] as an alternative method of estimating the parameters of interest.

For each drug (morphine, dexmedetomidine and the fixed-ratio mixture) 1000 bootstrap samples were drawn, a logit curve was fitted to each one, and the ED_{50} was calculated and converted from log dose to actual dose to give 1000 ED_{50} estimates for each drug or mixture. The bootstrapping was performed separately for each dose so that each bootstrap sample contained the same number of data points for each dose as the original data set but generally contained other than one of each of the originals: none of some, one of some, two of some, and so on. With 3–12 data points at each dose, this gave far fewer than 1000 different bootstrap samples for each dose, but far more than 1000 possible bootstrap combinations of the samples from all doses. Indeed, there was a small percentage of identical ED_{50} values in the set of 1000 bootstrap estimates for each drug.

Finally, random samples from the morphine and dexmedetomidine sets were combined to give a set of 1000 theoretical additive ED_{50} values which in turn were combined with randomly selected bootstrap ED_{50} values for the fixed-ratio mixture to obtain the difference which provides a measure of the degree of supra-additivity.

The sets of bootstrap ED_{50} values for the individual drugs and for the fixed-ratio mixture gave medians that were within 2% of the original fitted ED_{50} values; the confidence limits (means of the 25th and 26th; and of the 975th and 976th ordered bootstrap sets) were all closer than those obtained by the Fieller equation (±20% to ±30% of the mean *vs* ±25% to ±60%). The difference between the bootstrap and Fieller estimates was 2% for the theoretical additive ED_{50} (CL ±20% *vs* ±30%) and 5% for the difference between the actual and theoretical additive ED_{50}, for the fixed-ratio mixture (CL ±50% *vs* ±80% leading to a P value for evidence of supra-additivity of <0.001 instead of 0.02).

It seems safe to conclude that the confidence limits and P value in the body of the article are, if anything, conservative estimates.

Acknowledgement

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Effect of sevoflurane on spontaneous sympathetic activity and baroreflexes in rabbits

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Summary

Sevoflurane causes a decrease in mean arterial pressure (MAP). We have studied in anaesthetized rabbits its interactive effects on MAP, the autonomic nervous system and baroreflexes. During sevoflurane administration changes in renal sympathetic nerve activity (RSNA) and heart rate (HR) were observed: (1) when the normal decrease in MAP occurred; (2) when this was prevented by angiotensin II; (3) during a similar decrease in MAP induced by infusion of sodium nitroprusside (SNP) without sevoflurane administration; and (4) during pressor and depressor responses to phenylephrine and SNP. There was a reduction in MAP from 80 to 40 mm Hg after 1–4% sevoflurane without changes in HR, while RSNA remained unchanged only up to concentrations of 3% and was depressed by 37% ($P < 0.05$) with 4% sevoflurane. When MAP was maintained constant with angiotensin II, both HR and RSNA decreased, by 12% and 69%, respectively, after 4% sevoflurane ($P < 0.05$). A decrease in MAP of 40 mm Hg during infusion of SNP increased HR and RSNA by 22% ($P < 0.05$) and 150% ($P < 0.01$), respectively. At 2% sevoflurane, baroreflex sensitivity (i.e. ΔRSNA/ΔMAP and ΔHR/ΔMAP) was depressed by 36% and 57%, respectively, for the pressor effects of phenylephrine, and by 89% and 81%, respectively, for the depressor effects of SNP. We conclude that the baroreflexes continued to compensate for the effects of sevoflurane on sympathetic and cardiomotor activity with concentrations up to 3% and 4%, respectively. (*Br. J. Anaesth.* 1998; **80**: 68–72)

Keywords: anaesthetics volatile, sevoflurane; sympathetic nervous system; reflexes, barorecetor; rabbit

Sevoflurane causes a concentration-related haemodynamic depression, particularly of mean arterial pressure (MAP)[1] which normally activates baroreflexes to cause an increase in heart rate (HR) and sympathetic activity. Alternatively, sevoflurane could cause a decrease in HR and sympathetic activity as a result of its central effects. However, the peripheral, central and baroreflex effects of sevoflurane interact, but hitherto there has been little work on their relative contributions to its perceived effects on the circulation. For example, Saeki and colleagues showed that up to 1.25 MAC of sevoflurane did not produce significant changes in renal sympathetic nerve activity (RSNA) in rabbits.[2] In humans, sevoflurane, at concentrations of 0.4–1.2 MAC, did not affect sympathetic nerve activity supplying skeletal muscle.[3] Thus the limited data available could suggest that although sevoflurane depresses baroreflexes, they continue to respond to some extent to a reduction in MAP, thereby maintaining the observed stability of RSNA and HR.

In this study we have tested the hypothesis that baroreflexes, although depressed, maintain a response to a reduction in MAP sufficient to mitigate the depressant effects of clinically used concentrations of sevoflurane on the autonomic nervous system.

Materials and methods

GENERAL PROCEDURES

The study was approved by the UK Home Office (license PPL 90/00852). We studied 22 New Zealand White rabbits of both sexes, weighing 3.5–4.0 kg. Anaesthesia was induced with methohexital 10–15 mg kg^{-1} i.v. and maintained with 1% α-chloralose in an initial bolus dose of 30 mg kg^{-1} i.v., followed by a continuous infusion of 15–20 mg kg^{-1} h^{-1}. A tracheotomy was performed and the lungs were ventilated artificially (SLE 2000, SLE Ltd, UK) with oxygen-enriched air. Neuromuscular block was maintained using bolus doses of succinylcholine 2 mg kg^{-1} i.v. every 20–30 min. A femoral artery and vein were cannulated for recording arterial pressure, sampling of blood and infusion of 1% α-chloralose. The right and left marginal ear veins were cannulated, one for infusion of fluids and the other for administration of test drugs. Oesophageal temperature was measured with a thermistor (Yellow Springs Instruments, OH, USA) and maintained at 37–39°C using heating lamps under the surface of the surgical table when required. pH$_a$ and arterial blood-gas tensions were measured using a blood-gas analyser (Radiometer ABL 3, Copenhagen, Denmark), and were maintained constant and also within the ranges of pH$_a$ 7.30–7.40, Pa_{CO_2} 4.4–5.5 kPa and Pa_{O_2} 22.7–28.0 kPa by adjusting ventilation and occasionally, when necessary, administration of small doses of sodium bicarbonate. HR, MAP and RSNA were recorded continuously on a multi-channel recording

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system and stored on disk for later analysis (Maclab 8, ADInstruments, Australia). Concentrations of sevoflurane were measured with a Capnomac II (Datex, Helsinki, Finland).

RECORDING OF RSNA

The right kidney was exposed retroperitoneally by a left flank incision. A fascicle of the renal sympathetic nerves, alongside the renal artery, was isolated, desheathed and cut distally, immersed in a mineral oil pool and mounted on silver–silver chloride electrodes for recording sympathetic activity. Signals from sympathetic nerves were preamplified (Tektronix 122, Beaverton, OR) and displayed on an oscilloscope (Tektronix 565, Beaverton, OR), and also monitored by an audiospeaker. The amplified signals were rectified and integrated with a 100 ms time constant (Neurolog NL90, Hertfordshire, UK). Both amplified and integrated signals were displayed on an oscilloscope and plotted with a thermal recorder (Gould 1602, Essex, UK). The total electrical activity of the rectified and integrated signals during 20-s periods was measured in arbitrary units. Data for processing used the average of three measurements in each data set and were expressed as percentages of control values.

EXPERIMENTAL PROCEDURE

The preparation was allowed to stabilize for at least 30 min after completion of surgery. Twenty-two animals were allocated randomly to one of four groups. In group I ($n = 7$), sevoflurane (Abbott Laboratories Ltd, Queensborough, UK) was administered at 1.0%, 2.0%, 3.0% and 4.0% expired end-tidal concentrations, each for 20 min. In group II ($n = 5$), sevoflurane was administered as in group I but hypotension was prevented by infusion of angiotensin II 0.08–14 μg kg^{-1} min^{-1} (Sigma, Poole, Dorset, UK) and MAP was maintained within control values throughout. Measurements were made at the end of the 20-min period of administration at each concentration, and 30 min after sevoflurane withdrawal. Group III ($n = 5$) received infusion of 0.1% sodium nitroprusside (SNP) to lower MAP to 30–40 mm Hg after which it was discontinued. Observations of HR, MAP and RSNA were made every 5 min during infusions of SNP and also 30 min after it was discontinued. Subsequently, HR and RSNA data were collected from this group at MAP values comparable with those in group I induced by 1%, 2%, 3% and 4% sevoflurane and also after recovery. Animals in group IV ($n = 5$) were used to measure baroreflex sensitivity by observing pressor and depressor responses to bolus injections of phenylephrine 0.5, 1, 2 and 4 μg kg^{-1} i.v. and SNP 2, 4, 8 and 16 μg kg^{-1} i.v., respectively, to produce dose–response curves.

Maximum changes in HR (ΔHR), RSNA (ΔRSNA) and MAP (ΔMAP) in response to different pressor and depressor doses of phenylephrine and SNP, respectively, were observed during a control period and again 20 min after administration of 1% and 2% sevoflurane. Baroreflex sensitivity was evaluated by relating ΔHR or ΔRSNA and ΔMAP, and also by calculating the ratio of the maximum changes in HR and RSNA to the maximum changes in MAP (ΔHR/ΔMAP and ΔRSNA/ΔMAP) produced by the largest doses of SNP and phenylephrine.

ANALYSIS OF DATA

All data were expressed as mean (SEM). Statistical analysis was performed by analysis of variance (ANOVA) followed, where indicated, by paired t tests. $P < 0.05$ was considered to be statistically significant.

Results

HR, MAP AND RSNA

Examples of recordings of RSNA, from individual preparations, during administration of sevoflurane or SNP alone, and also during sevoflurane administration when a decrease in MAP was prevented by an infusion of angiotensin II, are shown in fig. 1.

The effects of sevoflurane and SNP on mean HR, MAP and RSNA are shown in fig. 2A and B. It can be seen that sevoflurane, which caused a reduction in mean MAP from 80 to 40 mm Hg at 4% sevoflurane, did not change mean RSNA with up to 3% sevoflurane which then decreased to 63% of control values at 4% sevoflurane ($P < 0.05$), without any significant change in mean HR from the mean control value of 246 beat min^{-1}. In contrast, when SNP induced a decrease in mean MAP from 80 to 40 mm Hg, there was an increase in mean HR from 249 to 292 beat min^{-1} ($P < 0.05$) and mean RSNA by 150% of control.

The effects of sevoflurane on HR and RSNA when hypotension was prevented by an infusion of angiotensin II 0.08–14 μg kg^{-1} min^{-1} are shown in fig. 2C. It can be seen that mean MAP was maintained near 84 mm Hg (i.e. the control value), HR remained unchanged with up to 2% sevoflurane but decreased from the mean control value of 259, to 239 beat min^{-1} and 231 beat min^{-1} at 3% and 4% concentrations of sevoflurane, respectively ($P < 0.05$). Mean RSNA decreased significantly to 75% ($P < 0.01$), 65% ($P < 0.01$), 57% ($P < 0.01$) and 39% ($P < 0.001$) of mean control values at 1%, 2%, 3% and 4% sevoflurane, respectively.

BAROREFLEX SENSITIVITY

Typical examples of recordings during phenylephrine 4 μg kg^{-1} i.v. and SNP 16 μg kg^{-1} i.v. injections showing the effect of sevoflurane administration at 1 and 2% are illustrated in figure 3.

Dose–response curves for changes in mean HR and mean RSNA in response to the pressor and depressor effects of phenylephrine and SNP, respectively, are shown in fig. 4.

For further clarification, the effects of 1% and 2% sevoflurane on ΔHR/ΔMAP and ΔRSNA/ΔMAP at the maximum effect in response to the highest doses of phenylephrine (4 μg kg^{-1}) and SNP (16 μg kg^{-1}) are shown in fig. 5. It can be seen that 1% sevoflurane reduced mean ΔHR/ΔMAP and ΔRSNA/ΔMAP by 24% (ns) and 30% ($P < 0.05$) for the pressor effects of boluses of phenylephrine, and by 56% ($P < 0.05$) and 42% ($P < 0.05$) for the depressor effects of boluses of SNP, respectively; at 2% sevoflurane, the

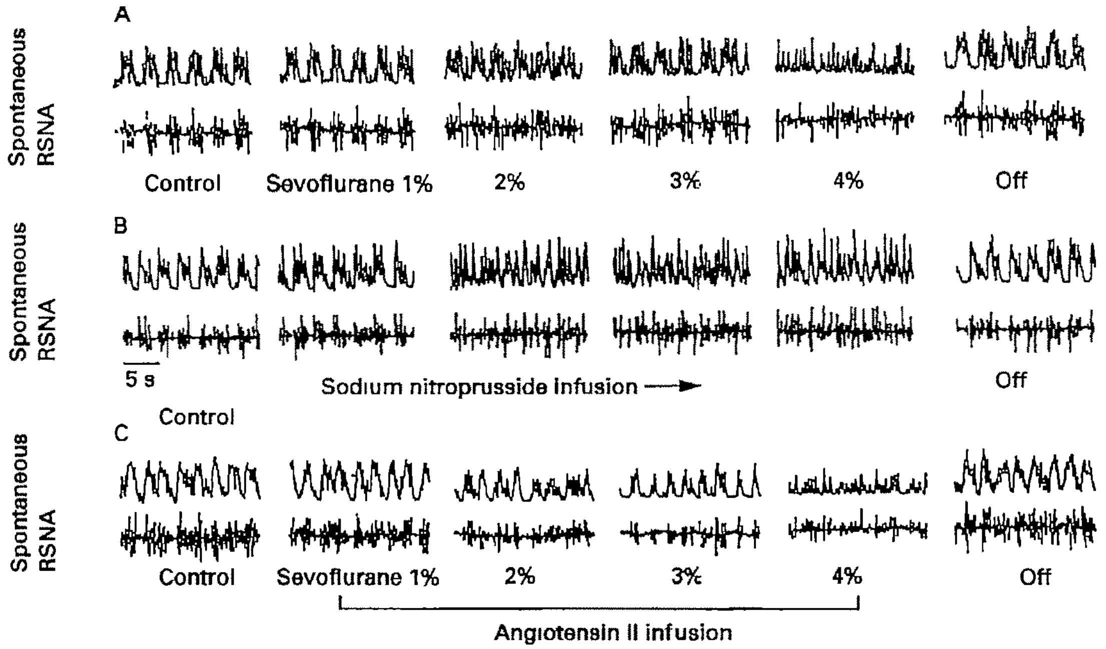

Figure 1 Example recordings of renal sympathetic nerve activity (RSNA) (lower traces, directly recorded RSNA; upper traces, rectified and integrated signals). A: Sevoflurane alone with an unmodified decrease in arterial pressure. B: Effects of sodium nitroprusside alone, at the same arterial pressures as those at equilibration with 1%, 2%, 3% and 4% sevoflurane, showing a typical baroreflex response with an increase in sympathetic activity. C: Effect of sevoflurane when the associated decrease in arterial pressure was prevented by infusion of angiotensin II.

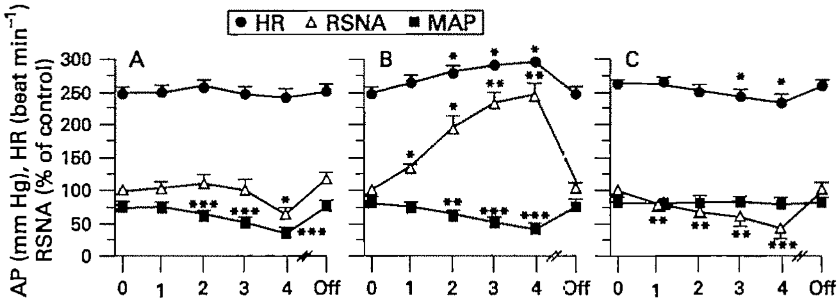

Figure 2 Effect of (A) sevoflurane ($n = 7$), (B) sodium nitroprusside (SNP) ($n = 5$) and (C) sevoflurane with angiotensin II i.v. ($n = 5$) on heart rate (HR), renal sympathetic nerve activity (RSNA) and mean arterial pressure (MAP) (mean (SEM)). B: Effect of SNP 0.5–8 μg kg^{-1} min^{-1} at comparable mean MAP values with those at equilibrium with 1%, 2%, 3% and 4% sevoflurane. C: Effect of sevoflurane on mean HR and RSNA when MAP values were maintained at control levels with infusions of angiotensin II 0.08–14 μg kg^{-1} min^{-1}. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ compared with control.

mean responses to phenylephrine were reduced by 57% for ΔHR/ΔMAP ($P < 0.01$) and 36% for ΔRSNA/ΔMAP ($P < 0.01$) and responses to SNP were reduced by 81% for ΔHR/ΔMAP ($P < 0.01$) and 89% for ΔRSNA/ΔMAP ($P < 0.01$).

Discussion

In this study 1–4% sevoflurane caused a concentration-dependent decrease in mean arterial pressure (MAP), without any significant change in mean heart rate (HR) while mean renal sympathetic nerve activity (RSNA), which remained unchanged up to 3% sevoflurane, decreased by 37% with 4% sevoflurane. In contrast, hypotension induced by sodium nitroprusside (SNP) caused major increases in both HR and RSNA. When the decrease in MAP, and hence compensatory baroreflexes, was prevented by angiotensin II, sevoflurane caused a progressive concentration-related depression of RSNA, but a significant decrease in mean HR occurred only at the highest concentrations of 3% and 4% sevoflurane. Although it was shown that sevoflurane caused a major reduction in baroreflex responses, it was concluded that they continued to compensate for its depressant effect on RSNA and HR with concentrations of up to 3% and 4%, respectively.

Saeki and colleagues reported that RSNA in rabbits was not influenced during sevoflurane administration up to 1.25 MAC.[2] A study in humans, in which direct recordings were made from nerve fibres in muscle sympathetic nerves, reported that the recorded activity remained unchanged during

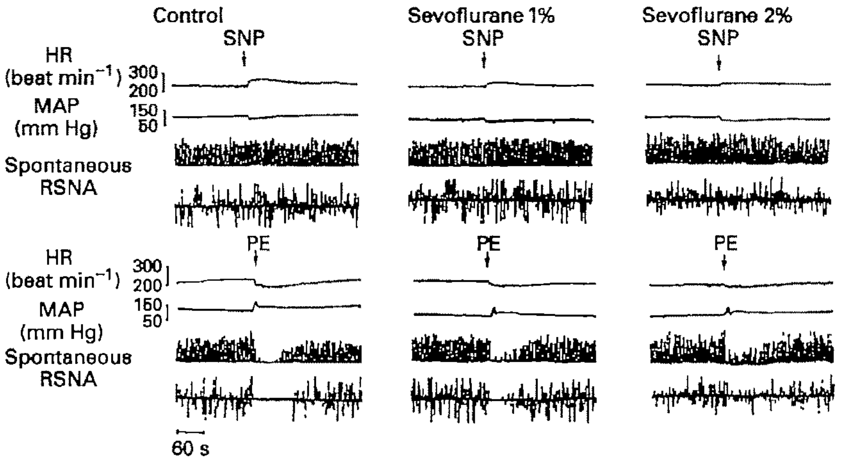

Figure 3 Example recordings of typical changes in heart rate (HR), mean arterial pressure (MAP) and spontaneous sympathetic nerve activity (RSNA· lower traces, directly recorded activity; upper traces, rectified integral) produced by the largest bolus injections of sodium nitroprusside (SNP) 16 μg kg⁻¹ i.v. and phenylephrine (PE) 4 μg kg⁻¹ i.v. (arrows), before and after equilibration with 1% and 2% sevoflurane.

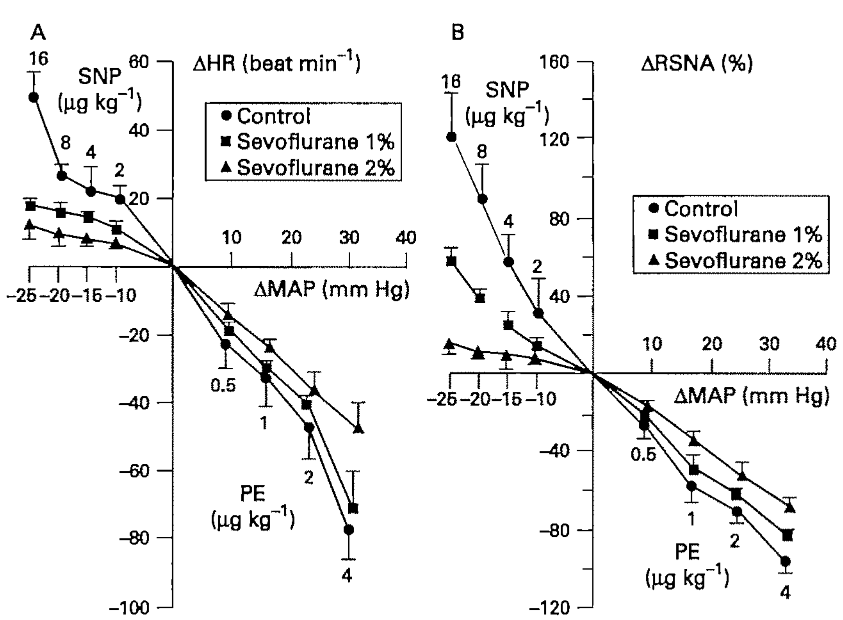

Figure 4 Relationship between ΔHR (A), ΔRSNA (B) and ΔMAP, caused by bolus injections of sodium nitroprusside (SNP) 2, 4, 8 and 16 μg kg⁻¹ i.v. and phenylephrine (PE) 0.5, 1, 2 and 4 μg kg⁻¹ i.v. before and after equilibration with sevoflurane in concentrations of 1.0% and 2.0% (mean (SEM), $n = 5$).

administration of sevoflurane in concentrations ranging from 0.4 to 1.2 MAC.[3] The results of our study showed that whereas concentrations of sevoflurane up to 3% (approximately MAC 1.5) caused no significant change in sympathetic activity, which is in keeping with previous work, a further increase to 4% (approximately 2 MAC) induced a significant reduction in RSNA.

Sevoflurane produced a concentration-related reduction in MAP, which is consistent with previous work.[1 4] Hypotension induced by sevoflurane results from both myocardial depression and a decrease in systemic vascular resistance.[1 5 6] Whereas a reduction in MAP caused by SNP induces typical baroreflexes with an increase in both RSNA and HR, the reduction in MAP caused by sevoflurane is not associated with such a response. When angiotensin II was used to maintain MAP constant, to examine the effects of sevoflurane uncomplicated by baroreflexes, it was found that sevoflurane caused a concentration-related depression of both RSNA and HR. However, previously it has been showed that angiotensin II itself may induce a degree of modification of baroreflexes.[7] For example the normal response to an increase in MAP, caused by peripheral vasoconstriction, is a decrease in both HR and sympathetic activity. During administration of angiotensin II in the rabbit, it has been shown that although there was a typical reduction in RSNA in response to the increase in arterial pressure,[8 9] it occurred without a significant change in HR.[7] In our study, when MAP was kept constant with angiotensin II, any observed changes in RSNA and HR could not be attributed to baroreflexes but indicated the unopposed direct effects of sevoflurane. Thus in the normal situation, without angiotensin II, a decrease in MAP would be expected to cause an increase in both RSNA and HR, which did not occur during sevoflurane administration in this study. However, although the studies when MAP was kept constant with angiotensin II clearly showed direct depression by sevoflurane of RSNA and HR, without further evidence one cannot comment on the degree of depression of the baroreflexes.

The effect of sevoflurane on baroreflexes was tested by observing the responses of RSNA and HR to the

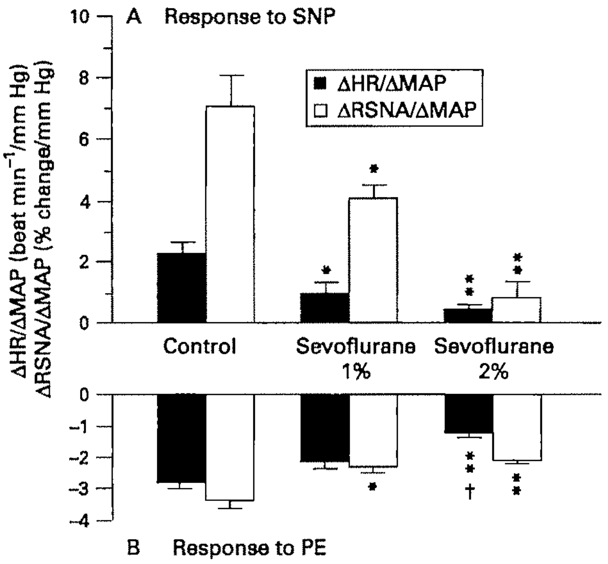

Figure 5 Changes in mean ΔHR/ΔMAP and mean ΔRSNA/ΔMAP induced by (A) sodium nitroprusside (SNP) 16 μg kg⁻¹ i.v. and (B) phenylephrine (PE) 4 μg kg⁻¹ i.v before and after equilibration with sevoflurane in concentrations of 1% and 2% (mean (SEM), $n = 5$). *$P < 0.05$, **$P < 0.01$ compared with control; †$P < 0.05$, 1.0% compared with 2.0% sevoflurane.

pressor and depressor effects of phenylephrine and SNP, respectively. It was demonstrated that baroreflex sensitivity, expressed as the relationship between changes in heart rate (ΔHR) and sympathetic activity (ΔRSNA), and ΔMAP (i.e. ΔHR/ΔMAP and ΔRSNA/ΔMAP ratios) was increasingly attenuated by an increase in sevoflurane concentration. However, whereas in depressor tests the ΔHR/ΔMAP ratio was depressed significantly throughout by sevoflurane, in pressor tests this ratio became significantly depressed only at the higher concentration of 2% ($P < 0.01$, fig. 5). These findings would support the traditional concept of Glick and Braunwald who suggested that whereas responses to increases in arterial pressure predominantly involved parasympathetic cardiomotor vagal activity, responses to decreases in arterial pressure were mediated principally by changes in sympathetic activity.[10]

In this study, the effect of sevoflurane at 3.0% and 4.0% on baroreflex sensitivity was not determined for two reasons. First, sevoflurane caused a major decrease in arterial pressure which prevented depressor tests without a serious risk to the viability of the preparations. Second, activity of the afferent fibres in the baroreceptor nerves is related to arterial pressure by sigmoid curves with the steepest part within the normal range of arterial pressures. This is reflected in rabbits in the relationship between RSNA and MAP which is also sigmoid and can be regarded as linear only for MAP values between 60 and 80 mm Hg.[11] Responses to changes in MAP outside this range do not provide a basis for comparison.

It is not known if there are specific sites in the baroreflex pathways which are depressed by sevoflurane. Saeki and colleagues suggested that sevoflurane, enflurane and isoflurane may act by direct depression of the central nervous system (CNS) or transmission in sympathetic ganglia rather than changes, for example, in the sensitivity of the aortic baroreceptors themselves.[2] Nevertheless, Seagard and co-workers reported that baroreceptor sensitivity is increased by both isoflurane and halothane.[12 13] From the data presented here it could be postulated that the absence of significant changes in RSNA at low concentrations of sevoflurane result from baroreflexes, albeit depressed, whereas the significant decrease in RSNA at higher concentrations is caused by direct depression of sympathetic pathways, for which the increasingly depressed baroreflexes can no longer compensate. Direct evidence of central depression was reported by Osawa and colleagues, who used the EEG to study the effect of sevoflurane on electrical activity in the CNS in cats and demonstrated that sevoflurane depressed the midbrain reticular neuronal activity in a concentration-dependant manner.[14] Although it has been reported that both halothane and isoflurane depress transmission in sympathetic ganglia,[12 13 15] as yet similar data have not been reported for sevoflurane.

In summary, although baroreflexes were depressed by sevoflurane, it appeared that they continued to compensate for the central depressant effects on RSNA up to concentrations of sevoflurane of 3% and cardiomotor activity up to 4%, which would provide an explanation for the apparent lack of effect of sevoflurane on the autonomic nervous system at low concentrations and validates the hypothesis tested in this study.

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British Journal of Anaesthesia 1998; **80**: 73–76

Effects of i.v. anaesthetic agents and halothane on [^{3}H]tetracaine binding to rat cerebrocortical membranes

M. KUDO, T. KUDO AND D. G. LAMBERT

Summary

In an attempt to determine if there is any overlap in local and general anaesthetic binding sites, we have examined the effects of thiopental, phenobarbital, pentobarbital, propofol, ketamine (racemic and R(+)/S(−)), alfaxalone, etomidate and halothane on [^{3}H]tetracaine binding to rat cerebrocortical membranes. Membranes were prepared in Tris HCl 50 mmol litre^{-1}, pH 7.4, by homogenization and centrifugation. Binding assays were performed in 1-ml volumes of Tris HCl buffer at room temperature or 37 °C for halothane. Binding of [^{3}H]tetracaine was displaced dose-dependently by unlabelled tetracaine with a mean pIC$_{50}$ value of 6.91 (SEM 0.07) (123 nmol litre^{-1}). With the exception of propofol (at high concentrations), all i.v. anaesthetic agents failed to displace the binding of [^{3}H]tetracaine. In contrast, halothane produced a dose-dependent and statistically significant reduction in total [^{3}H]tetracaine binding at clinically achievable concentrations (0.289, 0.885 and 1.484 mmol litre^{-1} equivalent to 1.0, 3.1 and 5.1 rat MAC) without markedly affecting the pIC$_{50}$. Collectively these data may suggest some overlap in the binding sites for [^{3}H]tetracaine and volatile but not i.v. general anaesthetic agents. (*Br. J. Anaesth.* 1998; **80**: 73–76)

Keywords: anaesthetics local, tetracaine; anaesthetics i.v.; anaesthetics volatile, halothane; model, rat; brain, cerebrocortex; theories of anaesthetic action, cellular mechanisms

We have shown previously dose-dependent and saturable binding of [^{3}H]tetracaine to rat cerebrocortical membranes. [^{3}H]Tetracaine binding was displaced dose-dependently by unlabelled tetracaine, procaine, lignocaine and prilocaine. Ropivacaine and bupivacaine were ineffective. In general, amino ester local anaesthetic agents displaced with the highest affinity.[1] In an attempt to determine the nature of the [^{3}H]tetracaine binding site we examined the effects of a range of ion channel blockers and neurotransmitters. With the exception of tetraethylammonium and 4-aminopyridine, all other non-anaesthetic agents failed to displace [^{3}H]tetracaine. These data may suggest an interaction with K$^+$ channels although it should be stressed that the interaction was weak.[1] Collectively these data confirm and extend previous studies using [^{3}H]tetracaine and [^{3}H]lignocaine[2–6] and imply that a single target site for all local anaesthetic agents is unlikely. To our surprise our previous study failed to show any displacement of [^{3}H]tetracaine with voltage-sensitive Ca^{2+} channel blockers,[1] despite the reported ability of local anaesthetics to displace [^{3}H]dihydropyridine binding to rat cerebrocortical membranes.[7]

In an attempt to further characterize the [^{3}H]tetracaine binding site we have examined the effects of a range of i.v. general anaesthetic agents (thiopental, phenobarbital, pentobarbital, barbituric acid, propofol, racemic ketamine, R(+) and S(−)ketamine, alfaxalone, etomidate) and the volatile anaesthetic agent halothane. The main aim of the study was to determine if there was overlap between the [^{3}H]tetracaine binding site and general anaesthetic binding site(s) in the CNS

Materials and methods

MEMBRANE PREPARATION

All studies were performed with membranes prepared from the cerebrocortex of female Wistar rats by homogenization and centrifugation, as described previously.[7 8] Briefly, the cerebrocortex was dissected from its internal structures, placed into Tris buffer 50 mmol litre^{-1}, pH 7.4, and homogenized using a Polytron (Maximum speed 3 × 10-s bursts) homogenizer. The resulting crude membrane homogenate was aliquoted at approximately 20 mg ml^{-1} and frozen until use (<2 weeks).

[^{3}H]TETRACAINE BINDING ASSAY

Binding of [^{3}H]tetracaine was performed in 1-ml volumes of Tris 50 mmol litre^{-1}, pH 7.4, for 1 h at room temperature.[1] (In halothane studies the incubation time was 45 min, see below.) Non-specific binding was defined in the presence of unlabelled tetracaine 1 mmol litre^{-1} and was typically less than 12%. The following agents were included in an attempt to displace [^{3}H]tetracaine binding: tetracaine 10^{-9}–10^{-5} mol litre^{-1}, thiopental 10^{-9}–10^{-4} mol litre^{-1}, phenobarbital 10^{-9}–10^{-3} mol litre^{-1}, pentobarbital 10^{-9}–10^{-3} mol litre^{-1}, barbituric acid 10^{-9}–10^{-3} mol litre^{-1}, propofol 1.5×10^{-9}–1.5×10^{-4} mol litre^{-1}, racemic ketamine 10^{-9}–10^{-3} mol litre^{-1}, R(+) and S(−)ketamine 10^{-9}–10^{-3} mol litre^{-1}, alfaxalone 10^{-9}–10^{-4} mol litre^{-1} and etomidate 10^{-9}–10^{-4} mol litre^{-1}. After incubation, bound and free radioactivity were separated by rapid vacuum filtra-

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Table 1 Aqueous halothane concentration following 45 min of pre equilibration at vaporizer settings of 1, 3 and 5 atm%, measured by gas chromatography and equivalent atm%. Data are mean (SEM) (n=5)

Vaporizer setting	Aqueous [halothane] (mmol litre^{-1})	Equivalent atm%
1	0.289 (0.003)	1.02 (0.01)
3	0.885 (0.027)	3.15 (0.10)
5	1.484 (0.013)	5.29 (0.05)

Table 2 Effects of a range of anaesthetic agents on [^{3}H]tetracaine binding to rat cerebrocortical membranes at 20 °C. Data are percentage displacement at the maximum dose used (mean(SEM))

Ligand	Maximum dose used	n	% Displacement
Tetracaine	10^{-5}	13	92 (2)
Thiopental	10^{-4}	6	0
Phenobarbital	10^{-3}	6	0
Pentobarbital	10^{-3}	6	9 (1)
Barbituric acid	10^{-4}	6	6 (3)
Propofol	1.5×10^{-4}	8	46 (1)
Racemic ketamine	10^{-3}	6	19 (3)
R(+) Ketamine	10^{-3}	6	14 (1)
S(−) Ketamine	10^{-3}	6	12 (4)
Alfaxalone	10^{-4}	6	12 (4)
Etomidate	10^{-4}	6	11 (4)

tion using a Brandel cell harvester onto Whatman GF/B filters. Filters were extracted overnight in Optiphase Safe prior to estimation of filter bound radioactivity.

VOLATILE AGENT DELIVERY

The effects of halothane were studied at 37 °C. Incubation buffer (0.9 ml) containing [^{3}H]tetracaine and unlabelled tetracaine were pre-equilibrated with halothane (1, 3 and 5atm% vaporizer setting) for 45 min using a 20-port manifold system to vented capped polypropylene tubes as described previously.[9] [10] Humidified air 2.0 litre min^{-1} delivered via a commercial aquarium pump was used as a carrier gas. The equilibration time of 45 min was determined empirically by measuring aqueous halothane concentrations at 1, 5, 10, 15, 30, 45 and 60 min at vaporizer settings of 1, 3 and 5atm% (n = 2, data not shown). Aqueous halothane concentrations (and equivalent atm% assuming that at 37 °C 1atm% would give an aqueous halothane concentration of 0.28 mmol litre^{-1}),[11] measured by gas chromatography[12] after a 45-min equilibration period are shown in table 1. After halothane equilibration, 100 µl of membranes (approximately 0.75 mg) were added and the incubation continued for another 45 min to allow the binding reaction to come to equilibrium, in the presence of either halothane or air. Bound and free [^{3}H]tetracaine were separated as described above. In all experiments a paired air and an ungassed control were included with each halothane concentration used.

DATA ANALYSIS

All data are presented as mean (SEM) (n). The concentration of displacing drug producing 50% displacement of specific binding (pIC$_{50}$) was estimated from individual curves by non-linear regression (GRAPHPAD-PRIZM).

Results

Binding of [^{3}H]tetracaine at room temperature was displaced dose-dependently by unlabelled tetracaine with a pIC$_{50}$ value of 6.91 (0.07) (123 nmol litre^{-1}), confirming our previous data (fig. 1).[1] With the exception of propofol at high doses (estimated pIC$_{50}$ 3.73 (0.02), 187 µmol litre^{-1}) all i.v. anaesthetic agents failed to displace binding of [^{3}H]tetracaine to rat cerebrocortical membranes (fig. 1, table 2).

Halothane produced a dose-dependent reduction in total specific [^{3}H]tetracaine binding compared with an ungassed control (fig. 2). There were no significant differences between total [^{3}H]tetracaine binding for ungassed control and paired air gassed control curves (halothane 0 mmol litre^{-1}, fig. 2D). Halothane produced a significant reduction in total binding at all (0.289, 0.885 and 1.484 mmol litre^{-1}) concentrations used. The pIC$_{50}$ was affected only by the highest concentration (1.484 mmol litre^{-1}, 5.29atm%), where a 1.63-fold rightward shift in the displacement curve was observed (table 3).

Discussion

We have demonstrated dose-dependent displacement of [^{3}H]tetracaine to rat cerebrocortical membranes by unlabelled tetracaine with a pIC$_{50}$ of 6.91 (0.07) (123 nmol litre^{-1}) consistent with previous reports.[1-6] With the exception of propofol (at high concentrations and hence with low affinity) all i.v. anaesthetic agents and barbituric acid failed to displace the specific binding of [^{3}H]tetracaine.

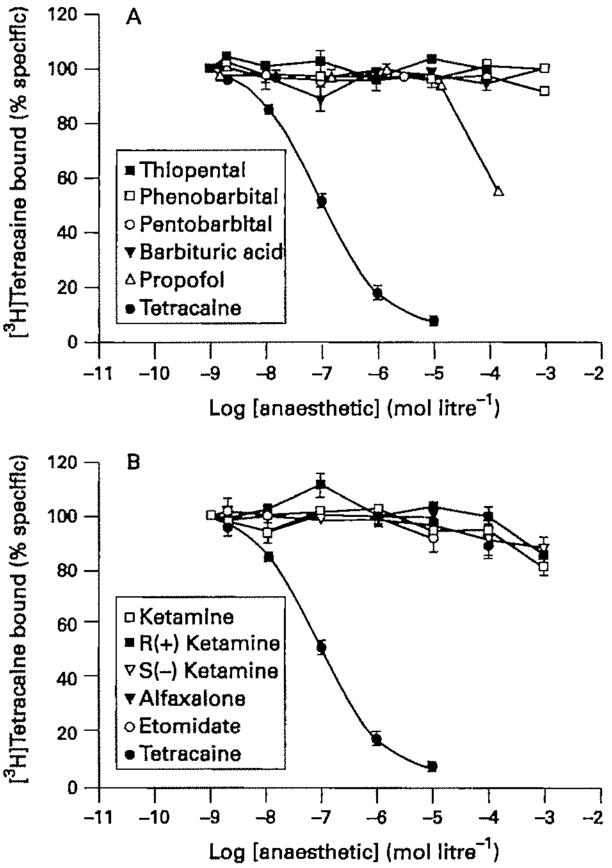

Figure 1 Effects of a range of anaesthetic agents on [^{3}H]tetracaine binding to rat cerebrocortical membranes. With the exception of tetracaine and propofol at high concentrations, there was no significant displacement. Data are mean (SEM) (n = 6–13) and all measurements were made at 20 °C.

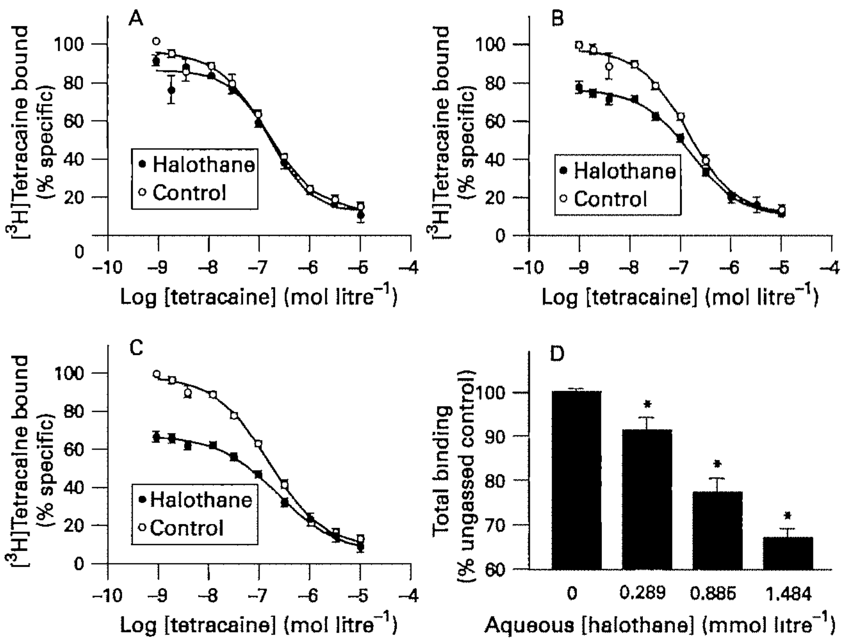

Figure 2 Effects of halothane on [^{3}H]tetracaine binding to rat cerebrocortical membranes Halothane produced a dose-dependent reduction (A: 0.289 mmol litre^{-1}, B: 0.885 mmol litre^{-1}, C: 1 484 mmol litre^{-1}) in total specific binding Data are mean (SEM) ($n = 6$) and all measurements were made at 37 °C. *$P < 0.05$, significantly reduced compared with paired air control

It is generally accepted that local anaesthetics depress neurotransmission by inhibiting neuronal Na$^+$ channels.[13, 14] However, it is also accepted that general anaesthetic agents do not produce significant Na$^+$ channel block and hence do not affect axonal conduction.[15] However, we have shown that [^{3}H]tetracaine was not displaced by tetrodotoxin (Na$^+$ channel blocker) and that a range of i.v. general anaesthetic agents also failed to displace [^{3}H]tetracaine. These data suggest that there is no direct overlap for the [^{3}H]tetracaine and i.v. general anaesthetic binding site(s). The voltage-sensitive Ca^{2+} channel represents a potential common target site for local and i.v. general anaesthetic agents. Both classes of agents inhibit the binding of [^{3}H]PN200–110 (a dihydropyridine) to L-type voltage-sensitive Ca^{2+} channels[7, 8] and inhibit Ca^{2+} flux through voltage-sensitive Ca^{2+} channels,[16, 17] although this is a controversial point that has received much attention.[17–19] This controversy is compounded by the observations that tetracaine displaces [^{3}H]dihydropyridine binding[7] when dihydropyridines fail to displace [^{3}H]tetracaine binding.[1]

In contrast with i.v. general anaesthetic agents, halothane at clinically achievable concentrations produced a clear and significant reduction in the binding of [^{3}H]tetracaine. However, the reduction in total specific binding at 1.02atm% (approximately 1.0 rat MAC[11]) was small (approximately 10%). The reduction in total specific binding without markedly affecting the pIC$_{50}$ (in the isotope dilution experiments presented in this study the IC$_{50}$ is equivalent to K_d as the concentration of [^{3}H]tetracaine was negligible) is consistent with halothane masking a proportion of the [^{3}H]tetracaine binding sites without affecting their binding properties. It is possible that [^{3}H]tetracaine could bind to two sites with differing sensitivity to halothane. However, close inspection of the curves in figure 2 do not support this notion as all had Hill slopes approaching unity. Volatile general anaesthetic agents interact with multiple targets within the CNS, including the well described GABA$_A$ receptor,[18, 20] excitatory transmission[21] and possibly voltage-sensitive Ca^{2+} channels.[17, 19] The data presented here suggest that there may be an overlap in the binding sites for volatile general anaesthetic agents and [^{3}H]tetracaine although the clinical relevance of these data are obscure.

Table 3 pIC$_{50}$ values for [^{3}H]amethocaine displacement curves in the presence and absence of halothane. Data are mean (SEM) (n=6). * $P < 0.05$ significantly greater than paired air control

Treatment	pIC$_{50}$	nmol litre^{-1}
Halothane 0.289 mmol litre^{-1}	6 81 (0 08)	155
Paired air control	6 69 (0 04)	204
Halothane 0 885 mmol litre^{-1}	6.84 (0 06)	143
Paired air control	6.87 (0.05)	135
Halothane 1 484 mmol litre^{-1}	6.61 (0 03)*	245
Paired air control	6.82 (0.03)	151

In conclusion, we have demonstrated that the binding of [^{3}H]tetracaine was unaffected by clinically relevant concentrations of i.v. general anaesthetic agents and reduced by halothane. The binding site or sites for [^{3}H]tetracaine remain to be determined and a “non-specific” binding site cannot be excluded.

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REVIEW ARTICLE

Cytokines and adhesion molecules in acute brain injury

E. G. McKeating and P. J. D. Andrews

Once thought to be relatively shielded from the immunological and inflammatory processes which occur in the tissues of other body systems after acute injury, the brain participates actively in these processes. As a result of trauma, haemorrhage or ischaemia, injury to the brain releases mediators such as the cytokines which activate inflammation and cause further secondary brain injury. Intensive care physicians can do little to alleviate the gravity of the primary injury, but by understanding the mechanisms responsible for secondary injury, and how these mechanisms may, in future, be altered by drug therapy, they may be able to improve patient management and outcome.

A primary brain injury stimulates the cells of the central nervous system (CNS) to produce a variety of mediators. Laboratory and human studies have shown that there are at least three important cytokines which are released both by microglia and astrocytes after injury: interleukin-1β (IL-1β), tumour necrosis factor α (TNFα) and interleukin-6 (IL-6).[67, 68, 82] These proteins function as intercellular communication molecules and stimulate the reparative process which is termed gliosis. Gliosis, however, results in further production and release of cytokines by hypertrophied astrocytes and microglial cells, in addition to mediators released by cells of the peripheral immune system, such as polymorphonuclear cells (PMN), which migrate across a "leaky" blood–brain barrier. The net result may therefore be further damage to brain tissue. The first part of this review focuses on the parts played by these cytokines.

Leucocyte adhesion molecules, which are expressed on the surface of leucocytes and endothelial cells, control the migration of leucocytes into tissue. The expression of these molecules after brain injury is linked closely to cytokine production. They mediate toxicity in two ways: by causing leucocyte plugging of micro-vessels and by facilitating the release of toxic oxygen-derived free radicals by PMN which migrate into brain tissue as a result of adhesion molecule activity. The second part of this review focuses on the parts played by the adhesion molecules, intercellular adhesion molecule (ICAM)-1, E-selectin, L-selectin, P-selectin and the integrins in brain injury, and on the evidence linking the cytokines to adhesion molecule upregulation. Finally, we shall discuss if anti-cytokine or anti-adhesion molecule therapy may improve outcome after acute brain injury.

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Keywords: polypeptides, cytokines; blood, adhesion molecules; brain, injury

Cytokines

The cytokines are low-molecular weight polypeptides which are synthesized and released by multiple cell types throughout the body. Their actions are numerous but they act primarily as mediators of the inflammatory process (either pro- or anti-inflammatory) and as growth factors. Many of the clinical signs which are seen after an acute brain injury (e.g. pyrexia, neutrophilia and cerebral oedema, secondary to disruption of the blood–brain barrier) are believed to be caused by cytokine activity.[76] Cytokines also stimulate the formation or release of many types of secondary mediators such as the oxygen-derived free radicals, neuropeptides and arachidonic acid derivatives, and upregulate the activity of the adhesion molecules. There is a great deal of overlap in the functions of these molecules, in particular between IL-1β and TNFα. Figure 1 summarizes the CNS actions of these cytokines.

INTERLEUKIN 1β AND TNFα

IL-1β and TNFα have similar local and systemic actions, which have been reviewed previously in the *British Journal of Anaesthesia*.[9, 91] Both cytokines have been implicated in the pathophysiology of disease states, including alcoholic liver disease, the systemic inflammatory response syndrome (SIRS), multiple trauma, burns and rheumatoid arthritis.[12, 24, 30, 63]

Experimental studies have shown that activity of both IL-1β and TNFα is increased within the first hours after a traumatic brain injury (TBI),[69, 102, 108, 111] and that microglia are a source of IL-1β,[33] which is a potent stimulant of gliosis.[34, 35] Cerebral IL-1β and TNFα are increased acutely after cerebral ischaemia in animal stroke models, particularly in the first hours after injury.[11, 60, 61, 100] These findings suggest that IL-1β and TNFα are released very early after injury, and explain partly why these two cytokines are often not detected in serum in clinical studies of brain injury.

Several laboratory studies have demonstrated the toxic effects of IL-1β and TNFα,[14, 71, 74, 105] although some investigators have used doses of cytokines well in excess of physiological concentrations. IL-1β acts to stimulate production of other cytokines, including TNFα,[18] and in particular IL-6, by both astrocytes and microglia.[2, 90] Similarly, TNFα causes the release of other cytokines, particularly IL-6.[2, 69, 90]

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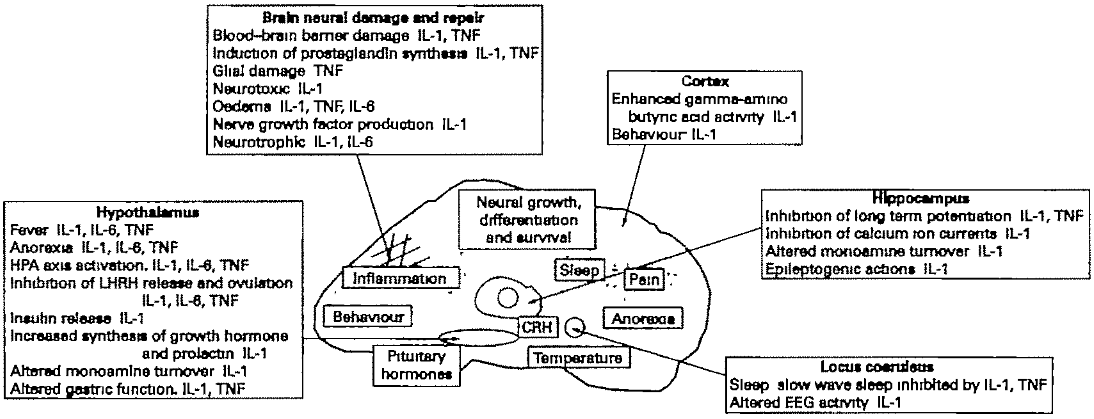
Brain neural damage and repair
Blood–brain barrier damage IL-1, TNF
Induction of prostaglandin synthesis IL-1, TNF
Glial damage TNF
Neurotoxic IL-1
Oedema IL-1, TNF, IL-6
Nerve growth factor production IL-1
Neurotrophic IL-1, IL-6
Cortex
Enhanced gamma-amino butyric acid activity IL-1
Behaviour IL-1
Hypothalamus
Fever IL-1, IL-6, TNF
Anorexia IL-1, IL-6, TNF
HPA axis activation. IL-1, IL-6, TNF
Inhibition of LHRH release and ovulation IL-1, IL-6, TNF
Insulin release IL-1
Increased synthesis of growth hormone and prolactin IL-1
Altered monoamine turnover IL-1
Altered gastric function. IL-1, TNF
Neural growth, differentiation and survival
Inflammation
Sleep
Pain
Behaviour
CRH
Anorexia
Pituitary hormones
Temperature
Hippocampus
Inhibition of long term potentiation IL-1, TNF
Inhibition of calcium ion currents IL-1
Altered monoamine turnover IL-1
Epileptogenic actions IL-1
Locus coeruleus
Sleep slow wave sleep inhibited by IL-1, TNF
Altered EEG activity IL-1

Figure 1 Cytokine actions within the brain. All actions attributed to the cytokines are included, some of which may not be present *in vivo*.

There are fewer clinical studies which have implicated either IL-1β or TNFα in brain injury. IL-1β is increased in the cerebral cortex[77] and IL-1β receptor concentration is increased in cerebrospinal fluid (CSF)[65] after spontaneous subarachnoid haemorrhage (SAH). IL-1β is increased in the CSF of patients who have sustained a stroke,[101] while McClain and colleagues found increased IL-1β concentrations in ventricular fluid after a traumatic brain injury.[67] Serum TNFα is increased in patients with meningococcal infection, and the increase is more marked in those who are hypotensive.[105] Goodman and colleagues showed increased serum TNFα in 21 patients with traumatic brain injury, but serum concentrations did not correlate with outcome,[36] while Ross and co-workers showed that TNFα was present in the serum of 18 of 50 patients with a TBI.[82]

It is therefore apparent that both IL-1β and TNFα are important factors in the propagation of the inflammatory process in the early stages after a brain injury. We shall discuss the effects of IL-1β and TNFα on adhesion molecule expression later in this review.

INTERLEUKIN-6

IL-6 differs from IL-1β and TNFα in that it both causes and inhibits inflammation.[76 85] Akira, Taga and Kishimoto have published a comprehensive review which covers its functions in detail.[1] A particularly important function of IL-6 in brain injury is its action in increasing endothelial permeability.[64] There has been some debate about whether or not IL-6 is an active mediator in the inflammatory process after tissue injury or is simply a marker of injury severity,[8] but the evidence clearly implicates IL-6 in the pathophysiology of inflammatory brain injury.

Hariri and colleagues found increased IL-6 production by cultured human astrocytes after fluid percussion injury[40] and Shohami and colleagues showed increased IL-6 concentrations in contused rat brain, which peaked 8 h after injury.[94] Other investigators showed similar increases in IL-6 in experimental trauma models,[102 108 111] which usually lag behind the production peaks of IL-1β and TNFα.

There are many clinical studies which have investigated the role of IL-6 in brain injury. Osuka and colleagues investigated the theory that increased serum concentrations of IL-6 were related to brain tissue damage, and measured IL-6 concentrations in the serum of 70 patients after neurosurgery. They found an increase which peaked 24 h after surgery.[75] In a similar study, Heesen and co-workers showed that serum concentrations of IL-6 were increased after craniotomy, peaking 24 h after operation.[41] In 30 patients with a TBI, McClain and colleagues found increased serum concentrations of IL-6, which were highest on admission, together with greatly increased ventricular fluid IL-6. The decrease in serum IL-6 concentration correlated with clinical improvement, and concentrations decreased more rapidly in those with a Glasgow Coma Scale score greater than 8.[68] A recent study of 22 patients with TBI found increased ventricular fluid concentrations of IL-6, and that there is an association between IL-6 concentration and production of nerve growth factor.[51] Our group in Edinburgh measured arterial and jugular venous concentrations of IL-6 in 32 patients who had sustained either a TBI or spontaneous SAH and found increased systemic IL-6 concentrations, together with a marked jugular venous–arterial difference.[70] This suggests significant intracranial production of IL-6 after brain injury, and supports the experimental work discussed earlier.[40 94]

Clinical studies in non-traumatic brain injury further implicate IL-6 as a mediator in the secondary inflammatory response. IL-6 concentration is increased in the serum and CSF of stroke patients.[5 50 101] IL-6 and IL-8 concentrations in CSF are increased after SAH, peaking on day 6.[47 65] An interesting study by Amado and colleagues found that the concentration of IL-6 in patients' plasma increases at the time of diagnosis of brain death.[3]

As we have already discussed, IL-1β and TNFα, together with many other mediators, including platelet activating factor, interferon and the bradykinins, promote IL-6 production. The part played by IL-6 in the regulation of the intracranial inflammatory process is complex, because it has pro- and anti-inflammatory actions, and has a negative feedback effect on the production of IL-1β and TNFα,[85] but it occupies a central point in the web of mediators which control the inflammatory response to brain injury.

OTHER CYTOKINES

There have been several other cytokines implicated in the secondary inflammatory response after brain injury. IL-8[76 84 91] may function as a neutrophil chemoattractant (chemokine) after brain injury[6,109]; a recent study showed that concentrations of IL-8 were increased in the CSF of patients who sustained a TBI, and that this was associated with nerve growth factor production.[52] Expression of the macrophage inflammatory proteins MIP-1 and MIP-2 is increased after brain injury,[49,88] and there is increasing interest in the physiological role of the growth factors, including transforming growth factor (TGFβ) and fibroblast growth factor (FGF) in the antagonism of the secondary inflammatory process.[4,15,44,46,57]

Adhesion molecules

The leucocyte adhesion molecules are important control factors in the pathophysiology of secondary brain injury. There are three families of adhesion molecules.[51] The first includes the glycoproteins, L-selectin, E-selectin and P-selectin. L-selectin is constitutively present on the surface of leucocytes, while E- and P-selectins are expressed on the endothelial cell surface after injury. P-selectin is also expressed on platelets. The glycoproteins mediate the initial tethering of leucocytes to the vessel wall by binding to counter-receptors within moments of tissue injury.[98] Deficiency of either the selectins or their ligands causes failure of the migration process and recurrent infection.[28]

The two other families mediate strong adhesion and migration across the endothelium into tissues. The immunoglobulin "superfamily" consists of ICAM-1, ICAM-2 and vascular cell adhesion molecule (VCAM) 1, which are present on the endothelial surface, and ICAM-3 which is present on the leucocyte cell surface. Their counter-receptors form the third family, the integrins (e.g. CD11b, CD18, Mac-1) (fig. 2). The blood of healthy humans contains soluble, active forms of the selectins and immunoglobulins (termed sL-selectin, sICAM-1).[86]

This review focuses on those molecules which have been studied most closely in brain injury, namely ICAM-1, E- and L-selectin and the integrins. As the functions of the three families are similar, we shall consider them as a group for the remainder of this review.

RELATIONSHIP BETWEEN CYTOKINES AND ADHESION MOLECULES

Experimental work suggests that IL-1β, IL-6 and TNFα upregulate the activity of the adhesion molecules: one early study showed that treatment of endothelial cell cultures with IL-1β caused increased PMN adhesion by acting on endothelial cells.[7] IL-1β increases ICAM-1 expression in fibroblasts, and IL-1β and TNFα increase ICAM-1 expression in hepatocyte cell lines.[27,54] Hahne and colleagues discovered that TNFα induced expression of several types of adhesion molecule in mouse endothelioma cells: ICAM-1, VCAM-1, E-selectin and P-selectin.[37] Kukielka and co-workers published findings on the relationship between IL-6 and upregulation of ICAM-1 in the pathophysiology of reperfusion injury in the myocardium.[53] They showed that IL-6 mRNA expression was increased in a canine myocardial reperfusion model, and that this was followed by an increase in ICAM-1 expression in the same segments. In a clinical study which examined 22 patients admitted to the ICU with illnesses resulting from liver cirrhosis, leucocyte expression of the integrins CD11b and CD35 correlated with the concentration of IL-6 in plasma.[81]

It is apparent therefore that the cytokines are important regulators of adhesion molecule activity in non-neurological disease, and further experimental studies which examined brain tissue add weight to this important relationship in brain injury. TNFα and interferon-gamma cause induction of ICAM-1 expression in microglia,[114] and administration of TNFα to cultured CNS endothelial cells causes increased expression of VCAM-1 and E-selectin.[26] Similarly, IL-1β ,TNFα, interferon-gamma and lipopolysaccharide (LPS or endotoxin) increase ICAM-1 expression.[107] Rieckmann and colleagues found increased expression of ICAM-1 in human brain tissue sections after stimulation with TNFα and LPS,[79] but Shrikant and co-workers were unable to show an effect of IL-6 on ICAM-1 expression in astrocytes or microglia.[95] Although findings are occasionally contradictory, they strongly suggest that the increased concentrations of cytokines seen after acute brain injury upregulate the activity of adhesion molecules in the CNS, causing PMN infiltration and further cellular damage (fig. 3). In the next section we examine more closely the adhesion molecules, and the part they play in brain injury.

ADHESION MOLECULES AND BRAIN INJURY

Clinical research into the role of adhesion molecules in disease is still in its infancy, particularly in acute brain injury, but many studies suggest that manipula-

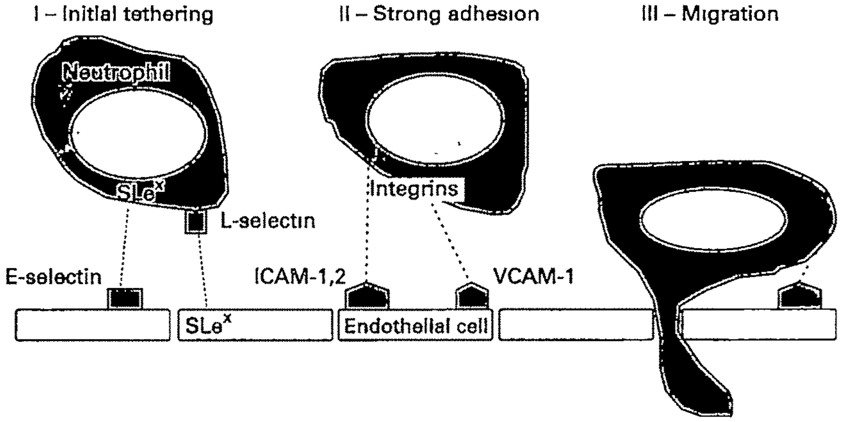

Figure 2 Stages of neutrophil adhesion to, and migration across, the endothelium.

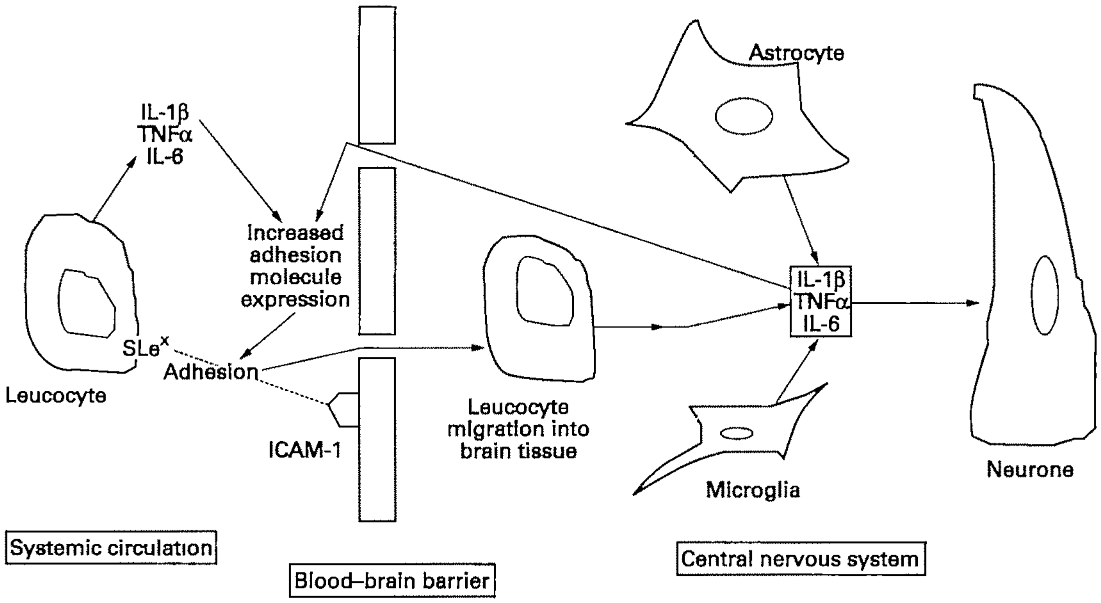

Figure 3 Intracranial cytokine and adhesion molecule interactions.

tion of the effects of these molecules may prove to be a powerful tool in the treatment of inflammatory disease. A review of the adhesion molecules by Froese and colleagues can provide additional background information.[51] The most extensively studied molecule is ICAM-1, a member of the immunoglobulin "superfamily". This molecule is expressed on the vascular endothelium and, as has already been stated, facilitates strong adhesion and migration of white cells from vessels into tissue. There is also evidence of its role in the intra-parenchymal binding of leucocytes to tissue cells such as astrocytes in the CNS.[92] The soluble forms of the adhesion molecules (e.g. sICAM-1) are those which can be measured by assay in the serum or plasma of normal individuals,[86] but the part they play in the physiological response to injury is unclear. Increased concentrations of the soluble endothelial molecules (sICAM-1, sE-selectin) may result from damage to the endothelium as a result of systemic inflammatory processes. Alternatively, these same processes may cause "activation" of the endothelium, with upregulation of production and shedding of these molecules into blood.[56] Investigators have explained changes in concentrations of the soluble form of L-selectin (one of the leucocyte bound molecules) in different ways,[23 99] which are discussed below.

Laboratory studies add weight to the evidence provided by the small number of clinical studies on this subject in brain injury. PMN accumulate in damaged brain tissue[32] and there is a significant correlation between the degree of PMN accumulation and the extent of cerebral oedema in rats.[87] There is little laboratory work on this subject in TBI; most studies have examined adhesion molecules in stroke models, although this work is certainly relevant to all forms of cerebral ischaemia. Wang and Feuerstein showed, in a rat stroke model, an increase in cortical E-selectin expression by 6 h after injury, which peaked at 12 h and returned to basal concentrations by day 5. ICAM-1 expression is also increased 3 h after injury and remains increased for 5 days.[106] Clark and colleagues studied CNS reperfusion injury in rats, with a temporary middle cerebral artery occlusion (MCAO) model. This important study showed an increase in cortical ICAM-1 expression from 1 h after injury. This correlated with moderate infiltration of PMN in the areas of ICAM-1 expression.[19] There is an upregulation of cortical E-selectin after cerebral reperfusion injury in primates,[39] and after SAH in rats there is increased expression of ICAM-1 on cerebrovascular endothelial cells.[38] Another recent study showed that ICAM-1 deficient mice were less susceptible to cerebral ischaemia/reperfusion injury.[97]

Many of the clinical studies on the subject of adhesion molecules carried out to date have been in the SIRS patient population. Cowley and co-workers found that serum concentrations of sICAM-1, sVCAM-1 and sE-selectin were increased in SIRS, particularly if there was multiple organ dysfunction (MOD).[23] A high sE-selectin concentration correlates closely with MOD and death.[23] Other studies also showed that sICAM-1[89] and sE-selectin[73] were increased in SIRS (concentrations of sICAM-1 were significantly higher after 24 h in non-survivors than survivors). Patients with multiple trauma have also been studied: an increase in serum sICAM-1 after multiple trauma correlated with the severity of subsequent MOD.[56]

There are only a small number of clinical studies which have investigated adhesion molecules in neurological disease and non-traumatic brain injury. ICAM-1 expression is increased in the cerebral vessels of patients with diagnoses of multiple sclerosis, viral encephalitis and cerebral infarct[96] and there is a high concentration of sICAM-1 in the CSF[42 80] and blood[42] of patients with bacterial meningitis, which correlates with measures of blood–brain barrier dysfunction.[80] Kim and colleagues studied leucocyte integrin expression in patients with a diagnosis of stroke or transient ischaemic attack and found increased expression of CD11a and CD18.[48] Lindsberg and co-workers studied brain sections of patients who had died from stroke disease and showed increased expression of endothelial ICAM-1.[59]

There are no published studies to date which have investigated serial changes in adhesion molecules in TBI or spontaneous SAH, but Keskil and colleagues reported that in a group of 153 patients with TBI there was a good correlation between injury grading and admission white cell count.[45] In a recent stroke study, Fassbender and colleagues found increased sICAM-1 and reduced sL-selectin concentrations in patients with significant risk factors for stroke, and in addition found increased sICAM-1, reduced sL-selectin, increased sE-selectin and sVCAM-1 concentrations in a group who had sustained a stroke.[29] This decrease in sL-selectin is explained by the notion that activated endothelial counter receptors "mop up" the "pool" of sL-selectin in serum. This theory supports the findings of Donnelly and colleagues.[25] They found reduced sL-selectin concentrations in the serum of a subgroup of patients who progressed to develop the acute respiratory distress syndrome from a sample judged to be "at risk" on recruitment to the study. Blann and colleagues proposed a similar theory to explain their findings of a reduced concentration of sL-selectin in patients with systemic sclerosis and vasculitis. They also showed an inverse relationship between serum sL-selectin concentration and disease severity.[10]

It is apparent therefore that acute brain injury causes increased expression of leucocyte adhesion molecules on cerebrovascular endothelium and in brain tissue itself, with expression mediated by cytokines. The final step in the investigative pathway is to examine the effects of cytokine and adhesion molecule antagonists on the process, and to examine if these compounds may potentially improve neurological outcome after brain injury.

Anti-cytokine and anti-adhesion molecule therapy

There are several questions to be answered in the final part of this review. What effects do anti-cytokine therapies have on cerebral tissues and expression of adhesion molecules after acute brain injury? Do monoclonal antibodies to adhesion molecules reduce secondary damage after a cerebral insult, and what effects do these potential therapies have in injuries to other organ systems? It is important, however, to consider that the cytokines function as natural communication molecules in host defence, and so antagonism of their actions may also have detrimental effects.

In experimental anti-cytokine therapy for brain injury, findings are encouraging. The increase in blood–brain barrier permeability and CSF white cell count caused by administration of intra-cisternal TNFα is abolished by treatment with a TNFα antibody.[55] Two studies examined the effects of anti-cytokine therapy on cerebral oedema: in a rat MCAO model, administration of an IL-1 blocker reduced cerebral oedema[110]; more recently, Shohami and co-workers showed that after TBI in the rat, administration of TNFα antibody caused a reduction in cerebral oedema and facilitated recovery of motor function.[93]

IL-1ra shows promise as a neuroprotective agent. Professor Nancy Rothwell's group in Manchester, provided what is probably the first direct evidence for cytokine involvement in brain injury when they showed that ischaemic and neurotoxic damage in the rat is inhibited by IL-1ra.[78] In a later study they gave IL-1ra to rats who had sustained a TBI. In the group where treatment was given immediately after injury, a reduction in lesion size, assessed histologically, of 44% was found. Even if treatment was delayed by 4 h, a 28% reduction in lesion size was seen.[103] Another approach to antagonizing the effects of IL-1β is to block the action of IL-1β converting enzyme (ICE), which converts the precursor molecule pro-IL-1β to its active form. Rothwell's group showed that administration of an ICE inhibitor reduced ischaemic brain damage in a rat model.[62]

Some workers have studied the effects of anti-cytokine therapy on adhesion molecule expression. In mice who have sustained a penetrating stab wound to the brain, treatment with antibody to IL-1 results in a significant reduction of ICAM-1 positive glia at 24 and 48 h after injury,[92] and cytokine specific antisera inhibit induction of ICAM-1 in adenocarcinoma cell lines by IL-1β and TNFα.[83] The evidence would therefore suggest that anti-cytokine therapy is indeed capable of reducing cerebral tissue damage and adhesion molecule expression after brain injury.

Finally, we should consider the therapeutic potential of blocking the actions of the adhesion molecules themselves. This will of course antagonize a natural body defence mechanism, and may in some cases be detrimental, but it is theoretically a more attractive option than attempting to block the diverse actions of the cytokines, with their complex inter-relationships. Clark and Zivin have recently published a detailed review on this subject in stroke disease,[22] but the subject has received little attention by investigators in TBI research.

Two groups have made substantial progress using models of CNS ischaemia. In 1991, Clark's group from Oregon published two articles[20 21] which examined the effects of anti-adhesion molecule antibodies in CNS ischaemia and showed that antibody to the integrin CD18 and to the immunoglobulin ICAM-1 produced a significant reduction in neurological deficits in a model of spinal cord ischaemia. This implicates leucocytes in CNS reperfusion injury. Zhang's group from Detroit has published findings from several studies in rat stroke models since 1994. They showed that antibody to various adhesion molecules reduces infarct size and PMN infiltrate.[16 43 112] In more recent work the group has looked at the effect of giving antibodies later than at the onset of ischaemia, which is much closer to the clinical situation. They showed that treatment with anti-integrin or anti-ICAM-1 antibodies several hours after the onset of ischaemia results in reduced infarct size.[17 113] Other groups have reported similar benefits.[58 66]

Other antagonists may have a part to play in future anti-adhesion therapy: heparin oligosaccharides bind to L- and P-selectin and thus inhibit their binding to other counter-receptors,[72] and inositol polyanions reduce binding of L- and P-selectin *in vitro*.[13]

This evidence suggests that administration of agents which antagonize the harmful effects of neutrophil adhesion and migration into tissue may reduce secondary brain injury in humans, although again we must be aware that adhesion and migration of leucocytes are natural responses of the host to injury, and that antagonism of these actions may reduce the positive effects of the inflammatory response. Phase three trials of an anti-ICAM-1 antibody are currently in progress in patients with stroke disease, and we await the results with great interest.

Conclusion

Research to date strongly implicates cytokines such as IL-1β, IL-6 and TNFα, together with the leucocyte adhesion molecules, in the pathophysiological response to primary brain injury. The cascades or webs of mediators released after primary injury cause secondary brain injury which may be severe. Prevention of systemic hypoxaemia, hypotension and hypothermia, together with optimization of oxygen delivery to the brain are priorities in the current intensive care management of acute brain injury.

Despite improvements in pre-hospital and intensive care, mortality and morbidity caused by traumatic brain injury has not decreased substantially in the past decade. Further work in the areas of anti-cytokine and, in particular, anti-adhesion molecule therapy may result in the clinical use of these novel therapies, which may alleviate the devastating secondary sequelae of an acute injury to the brain.

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SHORT COMMUNICATIONS

Effect of dexamethasone on postoperative emesis and pain

K. Liu, C. C. Hsu and Y. Y. Chia

Summary

In this double-blind, randomized, placebo-controlled study, we have evaluated the effect of preoperative administration of dexamethasone on postoperative vomiting and pain in 60 women undergoing general anaesthesia for major gynaecological surgery. Dexamethasone 10 mg (group D) or saline (group S) was administered i.v. in a double-blind manner during induction of anaesthesia. Postoperative pain relief was controlled with bolus doses of morphine using an i.v. patient-controlled analgesia device, and patients were assessed for incidence of vomiting, sedation score, verbal pain rating score, time to first morphine demand and morphine consumption at 4, 8, 12 and 24 h after surgery. Six patients in group D and 19 in group S experienced vomiting at least once within the 24-h postoperative period; dexamethasone was effective in reducing the overall incidence of vomiting from 63.3% to 20.0% ($P < 0.01$). Other variables were similar between the groups, and the influence of dexamethasone on postoperative pain was minimal.(*Br. J. Anaesth.* 1998; **80**: 85–86)

Keywords. pharmacology, dexamethasone; vomiting, nausea, postoperative; vomiting, incidence; pain, postoperative; analgesia, patient-controlled

In 1964, Smith and colleagues injected a steroid–penicillin–local anaesthetic mixture into the tonsillar fossae during surgery and observed a reduction in postoperative pain and inflammation.[1] In 1972, Papangelou compared oral dexamethasone, in combination with analgesics, with analgesics alone, in 480 patients undergoing tonsillectomy and found less tissue oedema and pain in the steroid-treated group in the postoperative period.[2] After the antiemetic effect of dexamethasone had been well established in patients receiving cancer chemotherapy in the 1980s, McKenzie and co-workers showed that ondansetron and dexamethasone were more effective than ondansetron and saline in the prevention of postoperative nausea and vomiting (PONV).[3] Recently, the antiemetic effect of dexamethasone alone was demonstrated successfully in paediatric tonsillectomy patients and ambulatory gynaecological patients.[4 5] Tissue injury-induced acute inflammation is known to play a significant role in the genesis of surgical pain, and dexamethasone should theoretically be beneficial in the management of acute surgical pain because of its potent anti-inflammatory effect. In this study, we have examined a single dose of dexamethasone 10 mg i.v. as an antiemetic and its influence on postoperative pain in adult patients undergoing major gynaecological surgery.

Methods and results

After obtaining approval from the Human Investigation Committee and informed patient consent, we studied 60 ASA I–II patients undergoing major gynaecological procedures. Anaesthesia was induced with fentanyl 5 μg kg^{-1} and diazepam 0.15 mg kg^{-1}; tracheal intubation was facilitated with lidocaine 1.5 mg kg^{-1}, thiopental 4 mg kg^{-1} and succinylcholine 1.5 mg kg^{-1}. General anaesthesia was maintained with halothane or isoflurane, 50% nitrous oxide in oxygen and i.v. infusion of atracurium. Before surgical incision, dexamethasone 10 mg or normal saline 2 ml was administered i.v. in a double-blind manner. At the end of operation, the trachea was extubated when the train-of-four ratio was greater than 75% without the aid of an anticholinesterase.

For postoperative analgesia, a PCA pump was programmed to deliver morphine 1.5 mg i.v. on demand with a lockout interval of 10 min, and pain intensity was rated by patients using a 0–10 verbal pain score (VPRS 0–10: 0 = no pain, 10 = most severe pain imaginable). Level of sedation was assessed by staff in the acute pain team using a 0–3 scale (0 = fully awake; 1 = asleep with response to stimulus; 2 = asleep without response to stimulus; 3 = comatose). Episodes of vomiting, VPRS, sedation score, time to first morphine demand and morphine consumption were recorded at 4, 8, 12 and 24 h after operation. Duration of hospital stay was also noted. Rescue antiemetic administration of prochlorperazine 10 mg i.m. was given at the patient's request. Data were analysed using the Student *t* test, chi-square test or Mann–Whitney *U* test, as appropriate, and are presented as mean (SEM). Statistical significance was assumed at $P < 0.05$.

There was no significant difference between groups in age, weight, height, ASA status, type and duration of surgery, duration of hospital stay, VPRS, sedation score, time to first morphine demand or morphine consumption (table 1). Emesis occurred in six of 30 (20.0%) patients in group D compared with 19 of 30 (63.3%) in group S ($P = 0.00738$). Among those who experienced emesis, all six of group D and

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Table 1 Postoperative morphine consumption (mg) (mean (SD))

Time after surgery (h)	Group D (n=30)	Group S (n=30)
4	3.1 (0.2)	3.4 (0.2)
8	5.6 (0.5)	6.5 (0.4)
12	8.1 (0.8)	9.5 (0.6)
24	14.4 (1.4)	16.9 (1.0)

Table 2 Number of patients who vomited. $^*P < 0.05$

Vomiting episodes	Group D (n=30)	Group S (n=30)	P
> 4	0	5*	0.02609
1-4	6	14*	0.02846
0	24	11*	0.00066
Incidence	20%	63.3%	
Patients received prochlorperazine	0	8*	0.00229

14 of group S patients had vomited no more than four times ($P = 0.02846$); the remaining five patients in group S vomited more than four times ($P = 0.02609$). The frequency of emesis in group S was significantly higher than that in group D (table 2).

Comment

The mechanism of dexamethasone-induced antiemesis is not fully understood, but central inhibition of prostaglandin synthesis[6] and decrease in 5-HT turnover in the central nervous system[7] or changes in the permeability of the blood CSF barrier to serum proteins[8] may be involved.[9] In contrast with the reported decreased wound pain following extraction of third molar teeth after dexamethasone administration,[9] the consistent reduction in morphine requirements observed in group D patients in this study was not significant ($P = 0.053$). Different postoperative pain intensities among these patients may be the major reason for this discrepancy. With its strong anti-inflammatory effect, dexamethasone should theoretically be beneficial for acute surgical pain, while for pain of lesser extent, its influence should be evident; for worse pain, its influence tends to be relatively small.

The number of patients required for this study was calculated to detect a difference in morphine requirements of 1.1 mg with a power of 90% at the 5% level of significance. Based on this, a minimum of 22 patients was required in each group. There were 30 patients in each group which implies that comparisons between groups were effective.

Dexamethasone is known to cause side effects such as increased incidence and severity of infection, adrenal suppression and delayed healing in surgical patients. The lack of difference in duration of hospital stay between groups implied that there was no additional wound infection or delayed healing accompanying dexamethasone usage. However, detailed investigation with a longer follow-up would be necessary to investigate this. The reported dose of dexamethasone for prevention of PONV is 0.15 mg kg^{-1}, up to a maximum of 10 mg i.v., yet favourable results were also noted with a single oral dose of dexamethasone 8 mg in adult patients.[9]

Among the antiemetics currently used, 5-HT antagonists (ondansetron, granisetron) are known to possess good antiemetic efficacy; however, their cost limits widespread clinical use. As emesis is not caused by a single mechanism at a specific site, studies with various combinations of antiemetics with different mechanisms of action may be promising. Dexamethasone, its with significant antiemetic properties and no evident adverse effects, may be a valuable constituent of combination antiemetic therapy.

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Changes in hepatocellular integrity during and after desflurane or isoflurane anaesthesia in patients undergoing breast surgery

P. TIAINEN, L. LINDGREN AND P. H. ROSENBERG

Summary

We have assessed hepatocellular integrity in patients anaesthetized with desflurane or isoflurane using glutathione transferase Alpha (GSTA) as a sensitive indicator. Volatile anaesthetic was administered to 72 women at 0.7 MAC for 25 min and thereafter at 1.0 MAC. GSTA was measured with a time-resolved immunofluorometric assay in serum samples. Mild or moderate increases in GSTA were found in approximately 40% of patients immediately after anaesthesia. In the desflurane group ($n = 30$) the increase in GSTA concentration was from a baseline value of the geometric mean of 1.3 μg litre^{-1} (95% confidence interval 0.9–1.9 μg litre^{-1}) to a peak of 2.6 (1.8–3.8) μg litre^{-1}. The corresponding increase in the isoflurane group ($n = 31$) was from 1.3 (0.9–1.9) μg litre^{-1} to 3.0 (2.2–4.2) μg litre^{-1}. The change in GSTA concentration was significant in both groups but not between groups. No predictive factors for the increase in GSTA concentrations were found. Increased GSTA concentrations were not accompanied by increases in aminotransferases. We conclude that desflurane and isoflurane anaesthesia were associated with a mild subclinical disturbance of hepatocellular integrity. (*Br. J. Anaesth.* 1998; **80**: 87–89)

Keywords: anaesthetics volatile, desflurane; anaesthetics volatile, isoflurane, enzymes, glutathione S-transferase; liver, function

We have found a mild disturbance in hepatocellular integrity during halothane,[1 2] sevoflurane,[1] isoflurane[2] and propofol anaesthesia[3] by measuring glutathione transferase Alpha (GSTA) in serum.[4] GSTA is a sensitive and rapidly reacting indicator of hepatocellular integrity.

Desflurane anaesthesia has generally not been associated with deleterious effects on the liver. Liver blood flow is well maintained during desflurane anaesthesia,[5 6] and its metabolism is minimal. Only one case of severe liver injury has been reported after desflurane anaesthesia[7] and it may be superior to other inhalation anaesthetics in this regard. Therefore, we measured serum GSTA concentrations after desflurane and isoflurane anaesthesia.

Methods and results

The study was approved by the local Ethics Committee and each patient gave written informed consent. Seventy-two women (aged 25–60 yr, ASA I–II) undergoing breast surgery were allocated randomly to receive either desflurane or isoflurane anaesthesia. Exclusion criteria, premedication, induction of anaesthesia, positive pressure ventilation, additional drugs, monitoring, postoperative observation and pain treatment were similar to the conditions in our previous study.[2] Desflurane or isoflurane were administered at 0.7 MAC (adjusted for age) for 25 min and thereafter at 1.0 MAC until the end of anaesthesia. At least 800 ml of Ringer's acetate solution were infused during anaesthesia according to blood loss and haemodynamics. Hydroxyethyl starch was infused when blood loss exceeded 400 ml. Relative hypotension was defined as a mean arterial pressure of less than 65% of baseline for more than 15 min and absolute hypotension as a mean arterial pressure of less than 60 mm Hg for more than 15 min. Decrease in arterial pressure was treated with i.v. fluids and temporary decrease of volatile anaesthetic to 0.8 MAC. Heart rate was classified as bradycardia (less than 60 beat min^{-1} for more than 40% of the duration of anaesthesia), normal (60–80 beat min^{-1} for more than 60% of the duration of anaesthesia) or tachycardia (more than 80 beat min^{-1} for more than 40% of the duration of anaesthesia).

Serum samples were collected before anaesthesia (baseline) and at 0, 1, 2, 4, 8, 20 and 44 h after the end of anaesthesia. GSTA was measured by a time-resolved immunofluorometric assay,[4] as described in our previous study.[2] Aminotransferases, glutamyl transferase and bilirubin were assayed in baseline samples. Aminotransferases were also measured 20 and 44 h after anaesthesia.

The assumptions for a power analysis were that a difference of 0.22 on log(10) scale (i.e. 40% under or 66% over the isoflurane group) is "clinically significant", that the SD is 0.3 on log(10) scale, and that 15% of patients have baseline GSTA concentrations more than 6.0 μg litre^{-1} and such patients are excluded. A power of 80% at $\alpha = 0.05$ required 36 patients in both groups.[8] Individual GSTA results were compared using repeated measures analysis of

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Table 1 Patient, anaesthesia, fluid management, and haemodynamic data (mean (range) or number of patients)

	Desflurane (n=30)	Isoflurane (n=31)
Patients		
Age (yr)	48 (35–58)	45 (25–60)
Weight (kg)	67 (51–95)	63 (50–80)
Height (cm)	167 (153–180)	165 (153–177)
Body mass index (kg m^{-2})	23.9 (17.4–29.4)	23.3 (18.0–28.4)
Anaesthesia		
Duration (min)	187 (92–450)	158 (90–292)
Thiopental (mg)	370 (250–600)	330 (250–450)
Fentanyl (μg)	400 (150–1550)	320 (150–850)
Nitrous oxide	3	2
Temporary 0.8 MAC	8	8
Blood loss and fluids		
Blood loss (litre)	0.45 (0.05–2.7)	0.39 (0.05–1.5)
Blood loss >500 ml	8	7
Ringer's solution (litre)	1.6 (0.8–4.0)	1.3 (0.9–3.0)
Hydroxyethyl starch	16	16
Transfusion	3	3
Haemodynamics		
Hypotension	11	11
Relative	8	9
Absolute	5	5
Bradycardia	8	7
Tachycardia	6	7
Hypotension and bradycardia	3	5

Table 2 GSTA concentrations (μg litre^{-1}) in serum, and area under the concentration curve (AUC) values (μg h litre^{-1}) (geometric mean (95% confidence interval)). Significant differences compared with baseline: *P<0.05, **P<0.01

	Desflurane (n=30)	Isoflurane (n=31)
Baseline (μg litre^{-1})	1.3 (0.9–1.9)	1.3 (0.9–1.9)
After anaesthesia		
0 h	1.8 (1.1–2.8)*	1.8 (1.3–2.6)*
1 h	1.6 (1.0–2.5)	2.1 (1.4–3.0)**
2 h	1.7 (1.2–2.5)	1.9 (1.3–2.7)*
4 h	1.4 (0.9–2.2)	1.5 (1.0–2.3)
8 h	1.0 (0.6–1.5)	1.5 (1.0–2.2)
20 h	1.6 (1.1–2.3)	1.5 (1.0–2.2)
44 h	1.5 (0.9–2.3)	1.2 (0.8–1.8)
Peak	2.6 (1.8–3.8)**	3.0 (2.2–4.2)**
AUC (μg h litre^{-1})	2.1 (1.1–4.2)	2.9 (1.5–5.8)

variance (ANOVA) techniques, as described previously.[2] The area under the curve (AUC) values for GSTA were measured by calculating the positive area over baseline from induction to 8 h after the end of anaesthesia. Peak and AUC values of GSTA were compared between groups using the *t* test. AUC values of GSTA were classified as low (<5 μg h litre^{-1}) and increased (≥5 μg h litre^{-1}) for log-linear analysis with arterial pressure, heart rate, blood loss (<500 ml *vs* ≥500 ml), administration of hydroxyethyl starch, addition of nitrous oxide, duration of anaesthesia (<180 min *vs* ≥180 min), age (<47 yr *vs* ≥47 yr) and body mass index (<24 kg m^{-2} *vs* ≥24 kg m^{-2}). The log-linear models were tested on two-way (each variable above and AUC) and three-way (volatile anaesthetic, each variable above and AUC) tables. Systat software was used for computing. Statistical significance was defined as $P < 0.05$.

The results of 61 patients were analysed. Reasons for exclusion were increased baseline GSTA in 10 patients and lost samples in one case. One patient underwent reoperation because of bleeding 5 h after the end of anaesthesia and her laboratory data 4, 8, 20 and 44 h after the initial anaesthesia were not included. The groups were comparable in patient and anaesthetic characteristics, fluid management, bleeding and haemodynamic data (table 1).

Changes in GSTA concentrations (table 2) were significant (repeated measures ANOVA) in the desflurane (P = 0.001) and isoflurane (P = 0.02) groups, but not between groups. Neither peak nor AUC values of GSTA differed between groups. Peak GSTA concentrations were greater than the reference range (0.7–6.0 μg litre^{-1}) in six patients in the desflurane group and in eight patients in the isoflurane group. Seven patients in the desflurane group and 10 in the isoflurane group had AUC values of 5–20 μg h litre^{-1}. AUC values of more than 20 μg h litre^{-1} were demonstrated in four and five patients, in the desflurane and isoflurane groups, respectively.

Three patients in the desflurane group and five patients in the isoflurane group exhibited a secondary peak of more than 3 μg litre^{-1} above baseline at 20 or 44 h after anaesthesia. One patient in the desflurane group, who underwent reoperation because of postoperative bleeding, exhibited a secondary peak of 101 μg litre^{-1} 8 h after the initial anaesthesia. Alanine aminotransferase concentrations also increased to 372 iu litre^{-1} and aspartate aminotransferase to 384 iu litre^{-1} 20 h after anaesthesia in this patient.

There was no significant association between the following variables and increased GSTA concentrations (log-linear model on two-way table) or between volatile anaesthetic, the following variables and increased GSTA (log-linear model on three-way tables): hypotension (P = 0.20 (two-way), P = 0.11 (three-way)), relative hypotension (P = 0.47, P = 0.37), absolute hypotension (P = 0.10, P = 0.30), bradycardia (P = 0.34, P = 0.38), hypotension and bradycardia (P = 0.27, P = 0.49), blood loss (P = 0.47, P = 0.52), administration of hydroxyethyl starch (P = 0.19, P = 0.51), addition of nitrous oxide (P = 0.42, P = 0.67), duration of anaesthesia (P = 0.38, P = 0.41), age (P = 0.63, P = 0.21) or body mass index (P = 0.92, P = 0.56). There was a minimal decrease in aminotransferase activities after anaesthesia.

Comment

We found a temporary increase in GSTA that was similar in both desflurane and isoflurane groups and comparable with our earlier studies.[1–3] The mechanisms of mild disturbance in hepatocellular integrity during or immediately after anaesthesia are still unclear. General haemodynamic depression is probably not the explanation for GSTA release because hypotension or bradycardia were not associated with increased GSTA concentrations. Local haemodynamic differences could be involved but hepatic blood flow is better maintained and autoregulation is probably more intact during isoflurane or desflurane anaesthesia than during halothane anaesthesia.[5 6] The possible influence of surgery on hepatocellular integrity cannot be excluded, but all operations in the present and two previous studies[2 3] were performed at superficial sites. Positive pressure ventilation may disturb hepatocellular integrity as has been demonstrated during halothane and isoflurane anaesthesia.[9] It is doubtful if this is a universal finding as an increase in GSTA has been found after sevoflurane anaesthesia with positive pressure ventilation[1] and with spontaneous ventilation.[10]

Eight patients exhibited a similar secondary increase in GSTA, as seen in previous studies.[1 2] However, only the patient whose peak GSTA concentration was 101 μg litre^{-1} after hypovolaemia and reoperation was shown to have developed more advanced, transient liver injury, as indicated by increased activities of aminotransferases. Peak concentrations of GSTA in this patient would probably have been considerably higher than those observed if blood samples had been collected more frequently during and after reoperation. The short half-life of GSTA in serum is a great advantage for demonstration of active liver injury. On the other hand, it is also a major limitation because it is impossible to estimate the peak or AUC values of GSTA if sampling is delayed.

The mild disturbance in hepatocellular integrity that appeared in the present and previous studies[1–3] seems to be unpredictable and without any clinical significance in most cases. However, it might have some clinical significance in the patient who underwent reoperation in this study and in two patients whose GSTA peaks were more than 300 μg litre^{-1} after halothane anaesthesia in the previous study.[2] Mild or moderate increases in GSTA (peak less than 50 μg litre^{-1}) commonly occur immediately after general anaesthesia without any clear difference between anaesthetics. These small changes are transient and not associated with clinical liver pathology.

We conclude that desflurane anaesthesia was accompanied by a minor increase in GSTA concentration of the same magnitude as that after isoflurane anaesthesia and has no clinical significance.

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5-Hydroxytryptamine causes depression of twitch height in the partially curarized rat phrenic nerve hemidiaphragm preparation

A. T. HINDLE AND P. M. HOPKINS

Summary

5-Hydroxytryptamine (5-HT) has significant effects on the skeletal neuromuscular junction. We have evaluated the potential neuromodulatory effects of 5-HT on the rat hemidiaphragm using a non-fatiguing pattern of stimulation (0.3 Hz) in a partially curarized preparation using tubocurarine (EC_{50} = 560 (range 400–650) nmol litre^{-1}). 5-HT was added to the partially curarized preparation in the following concentrations: 0, 12.5, 25, 50, 100, 200 and 400 nmol litre^{-1} and the twitch response was recorded at each concentration. These measurements were expressed as a ratio of control values, plotted against time and the area under the curve (AUC) calculated. The AUC values for test and control hemidiaphragms were compared by paired *t* test analysis accepting a 5% significance level. The mean AUC for test (3327 mm^2) and control (4102 mm^2) preparations were significantly different ($P = 0.003$). We have shown that the addition of low concentrations of 5-HT to the indirectly stimulated partially curarized rat diaphragm preparation caused depression of twitch height. (*Br. J. Anaesth.* 1998; **80**: 90–91)

Keywords: serotonin (5-hydroxytryptamine); neuromuscular block, measurement of response; neuromuscular block, tubocurarine; rat

5-Hydroxytryptamine (5-HT) is released from the nerves innervating skeletal muscle preparations[1] where it may modulate the action of acetylcholine. High concentrations of 5-HT (millimolar) exhibit depressant effects on single twitch responses of skeletal muscle preparations.[2 3] Previous workers have suggested that the reduction in twitch height produced by 5-HT may be a result of a curare-like effect on the motor end-plate of skeletal muscle[4] but have failed to demonstrate that 5-HT exhibits a curare effect on skeletal muscle at resting rates of stimulation.[5] When 5-HT is applied at bath concentrations in excess of 5 mmol litre^{-1}, necrotic effects have been observed in *in vitro* skeletal muscle preparations.[6] In order to examine the interactions of 5-HT with neuromuscular blocking agents we tested the following null hypothesis: 5-HT has no effect on twitch responses of the vertebrate skeletal muscle where the safety factor for transmission at the neuromuscular junction has been reduced by application of tubocurarine. We investigated the effects of 5-HT added cumulatively (0–400 nmol litre^{-1}) to a partially curarized rat phrenic nerve diaphragm preparation.

Methods and results

Male Wistar rats (200–300 g) were used as a source of phrenic nerve diaphragms. The diaphragms were dissected out after the animals were killed by stunning and decapitation. Excess tissue was removed from the dissected diaphragms which were placed subsequently in a tissue bath containing oxygenated (95% oxygen–5% carbon dioxide) Krebs solution maintained at 37 °C. The diaphragms were pre-tensioned to 4 g and stimulated indirectly at supramaximal voltage (4–12 V). A Digitimer DS9A stimulator was set to deliver electrical stimuli with a pulse width of 0.5 ms and frequency of 0.3 Hz. No licence was needed as animals were killed under schedule 1 of the Animals (Scientific Procedures) Act 1986.

Responses were recorded isometrically, transduced (Ormed 4157) and displayed on a Windograf recorder (Gould Instruments). The recording apparatus was calibrated at the start of each experiment. This was carried out by suspending pieces of metal of known weight (0.5 g, 1 g) from the arm of the transducer and recording the deflection on the Windograf display up to a total of 4 g deflection.

Tubocurarine was added cumulatively in 200-nmol litre^{-1} increments and twitch height was allowed to stabilize between addition of one concentration and the next. This was continued until all twitches were abolished. The excitatory concentration which produced 50% (EC_{50}) depression of twitch height was calculated. The hemidiaphragms were exposed to a standardized wash cycle and allowed to equilibrate for 30 min. The EC_{50} dose of tubocurarine was added to the preparation and the twitch response allowed to stabilize.

5-HT (Ciba Geigy) was added cumulatively to one hemidiaphragm preparation in the following concentrations: 12.5, 25, 50, 100, 200 and 400 nmol litre^{-1}, while an equal volume of control solution (Krebs) was added to the contralateral diaphragm which acted as a time-matched concurrent control. Five minutes were allowed between successive additions of each concentration of 5-HT.

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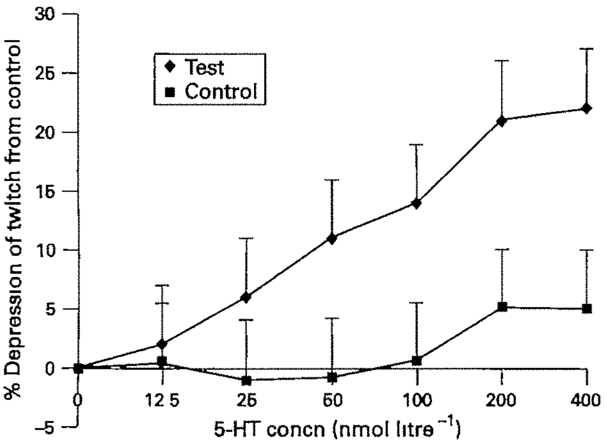

Figure 1 Effects of 5-HT on the partially curarized diaphragm. The X axis refers to the concentration of 5-HT, each individual concentration being added cumulatively. The Y axis refers to the percentage depression of twitch height from baseline. In this instance "baseline" refers to the twitch height of the partially curarized preparation before addition of 5-HT. Data are mean (SEM).

The twitch response of the hemidiaphragm after addition of tubocurarine acted as the reference value against which all other twitch responses, after addition of 5-HT or control, would be compared. Twitch height after addition of each concentration of 5-HT was recorded and expressed as a ratio over the reference value. The recordings from the contralateral diaphragm (time-matched concurrent control) were treated in the same way. The ratios were plotted subsequently against time for each experiment. The area under the curve (AUC) of the time ratio response relationship was calculated and the values of the areas for test and control preparations were compared by paired *t* test analysis accepting a 5% level of significance. For presentation purposes the data have been presented in the form of a concentration–response relationship.

There was consistent depression in twitch height in the preparation treated with 5-HT compared with controls ($n = 7$). A plot of change in twitch response over time indicated that the mean areas were significantly different between treatment and control groups ($P = 0.003$). The results for the seven pairs of experiments are summarized in figure 1.

Comment

In this study we have demonstrated that 5-HT depressed the twitch response in a partially curarized preparation when added at low concentrations (12.5–400 nmol litre^{-1}) but had no effect in the absence of tubocurarine at the same concentrations. This would imply that the presence of tubocurarine compromised the interaction of acetylcholine with its receptors at the neuromuscular junction in such a way that 5-HT was able to evoke a depressant effect on the indirect twitch response of skeletal muscle. This could imply that 5-HT was either depressing the release of acetylcholine from the presynaptic terminal or reducing postsynaptic sensitivity to the effects of acetylcholine. To the best of our knowledge this has not been demonstrated previously. However, previous studies carried out by us have shown that 5-HT can modulate the twitch responses of the indirectly stimulated rat diaphragm during tetanic stimulation.[7] In this situation it is possible that 5-HT is able to modulate twitch responses when the processes involved in acetylcholine replenishment are maximized.

We feel that these observations need further examination using a range of selective 5-HT agonists and antagonists in order to identify the receptor or receptors involved in the action of 5-HT. Further investigation is also required to help formulate a basis for possible interactions with other drugs already known to be active at the neuromuscular junction.

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CASE REPORT

Use of methadone in the morphine-tolerant burned paediatric patient

P. I. WILLIAMS, R. E. SARGINSON AND J. M. RATCLIFFE

Summary

We describe the successful use of methadone in the restoration of sedation and provision of analgesia in two morphine-tolerant, paediatric patients who had suffered significant thermal injuries and were undergoing mechanical ventilation. Both patients had exhibited escalating requirements for sedative drugs while undergoing ventilation yet remained inadequately sedated. The introduction of i.v. methadone in place of i.v. morphine in the sedative regimen rapidly and effectively restored a state of sedation. Hyperalgesia and morphine tolerance appear to be associated; it is proposed that methadone acts primarily, under these circumstances, by re-establishing the analgesic state. Such use of methadone in the morphine-tolerant patient also afforded a concomitant sedative-sparing effect. (*Br. J. Anaesth.* 1998; **80**: 92–95)

Keywords: analgesia, paediatric; sedation; intensive care, sedation; analgesics opioid, methadone

Case report

PATIENT NO. 1

An 18-month-old female, weighing 12 kg, was admitted to the regional paediatric intensive care unit (PICU) with 70% cutaneous burns of both partial and full thickness involving the face, neck, trunk and limbs. Additionally, there were airway burns and smoke inhalation injury. Tracheal intubation had been undertaken and intermittent positive pressure ventilation (IPPV) commenced before admission to the PICU; mechanical ventilation was continued throughout her admission. She underwent several surgical procedures of varying complexity for her burns. However, it became evident that survival would be most unlikely because of the severity of her initial injury and subsequent failure of skin engraftment. The child died on day 62. Throughout her stay in the PICU, her requirements for sedative drugs increased, gradually at first and then in a dramatic manner. The sedative regimen used, and the necessary changes made to it, are presented in table 1.

On day 49, at the time of stopping the i.v. morphine infusion, blood sampling was performed for assay of concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide. The respective concentrations were subsequently reported as follows: morphine 202 nmol litre^{-1}, morphine-3-glucuronide 1308 nmol litre^{-1} and morphine-6-glucuronide 527 nmol litre^{-1}.

Table 1 Patient No. 1: sedative regimen used and necessary changes to this regimen

Day	Sedative requirements
Admission	I.v. infusions of midazolam 80 μg kg^{-1} h^{-1} and morphine 40 μg kg^{-1} h^{-1} instituted with i.v boluses of vecuronium 1 mg as required to ensure compliance with mechanical ventilation
11	With midazolam and morphine being infused i v. at doses of 100 μg kg^{-1} h^{-1} and 60 μg kg^{-1} h^{-1} respectively, promethazine 12 mg via the nasogastric (n.g.) route at regular 6-h intervals (qds) was added as a sedative adjunct
13	N.g. chloral hydrate 600 mg qds, was introduced to the existing regimen to ensure acceptable sedation
28	The sedative regimen now comprised i.v. midazolam 750 μg kg^{-1} h^{-1}, i.v. morphine 480 μg kg^{-1} h^{-1}, n.g promethazine 12 mg qds, and n.g. chloral hydrate 600 mg qds
35	Secobarbital was added at a dose of 50 mg twice daily (bd) via the n.g. route
38	It became necessary to add ketamine via i.v. infusion, the starting dose being 90 mg h^{-1}
39	I.v. ketamine was reduced to 35 mg h^{-1}
49	The sedative regimen comprised i.v. midazolam 2 mg kg^{-1} h^{-1}, i.v. morphine 390 μg kg^{-1} h^{-1}, i.v. ketamine 35 mg h^{-1}, n.g. promethazine 12 mg qds, n.g. chloral hydrate 600 mg qds and n.g secobarbital 50 mg bd. However, the child was restless, repeatedly attempting to remove her nasotracheal and nasogastric tubes, and non-compliant with a synchronized intermittent mandatory ventilation mode Additional bolus doses of midazolam 5 mg afforded only transient tranquillity. It was decided to substitute methadone for morphine. Morphine was stopped and an i.v. loading dose of methadone 2.75 mg kg^{-1} was administered over a period of 60 min, followed by an i.v. infusion of methadone 325 μg kg^{-1} h^{-1} which was maintained for the next 24 h. Simultaneously, i.v midazolam was reduced to 1.4 mg kg^{-1} h^{-1} and i.v ketamine to 25 mg h^{-1}
50	The methadone dosage was then rationalized to 20 mg i v. thrice daily (tds), with each dose being administered over a 10-min period
53	Both ketamine and secobarbital were stopped and methadone reduced to 20 mg i.v. bd.
55	Effective sedation was provided by i.v. midazolam 830 μg kg^{-1} h^{-1}, methadone 20 mg i.v. bd and chloral hydrate 600 mg n g qds. Promethazine 12 mg n g qds was continued empirically for its antipruritic effect

PATIENT NO. 2

A 6-yr 2-month-old female, weighing 20 kg, was admitted to the regional PICU with 48% full thickness burns involving the trunk, waist, thighs and arms. Tracheal intubation had been undertaken and IPPV commenced before admission to the PICU; mechanical ventilation was continued. Subsequently, several surgical procedures were undertaken for her burn injuries. During her stay in the PICU, her sedative requirements escalated. The sedative regimen used, and the changes made to it, are presented in table 2.

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Table 2 Patient No. 2: sedative regimen used and necessary changes to this regimen

Day	Sedative requirements
Admission	I.v. infusions of midazolam 32 $\mu g\ kg^{-1}\ h^{-1}$ and morphine 20 $\mu g\ kg^{-1}\ h^{-1}$ commenced producing satisfactory sedation
5	The sedative regimen now comprised i.v. midazolam 200 $\mu g\ kg^{-1}\ h^{-1}$ and i.v. morphine 200 $\mu g\ kg^{-1}\ h^{-1}$
7	N.g. promethazine 12 mg qds and n.g. chloral hydrate 500 mg qds were added. I.v. midazolam was being infused at 500 $\mu g\ kg^{-1}\ h^{-1}$ with i.v. morphine at 160 $\mu g\ kg^{-1}\ h^{-1}$
10	The dose of i.v. morphine had been increased to 320 $\mu g\ kg^{-1}\ h^{-1}$ yet sedation remained inadequate. Therefore, it was decided to introduce methadone in place of morphine. The initial dose of methadone was 5 mg i.v. bd, the dose being administered over a period of 10 min
14	It was necessary to increase the dose of methadone to 5 mg i.v. tds
16	Increasing the daily dosage of methadone permitted a reduction in the dose of i.v. midazolam to 100 $\mu g\ kg^{-1}\ h^{-1}$
17	Weaning from mechanical ventilation was commenced. Midazolam was withdrawn, the dose of methadone reduced to 4 mg i.v. tds, and both promethazine and choral hydrate maintained at 12 mg n.g. qds, and 500 mg n.g. qds, respectively. Acceptable sedation was afforded by these doses
26	A further skin engraftment procedure led to the dose of methadone being restored to 5 mg i.v. tds
27	Mild agitation was apparent which responded readily to increasing chloral hydrate to 1 g n.g. qds
29	The trachea was extubated and the dose of methadone was switched from 5 mg i.v. tds to 8 mg n.g. tds; simultaneously, the dose of chloral hydrate was reduced to 500 mg n.g. qds and promethazine stopped. Spontaneous ventilatory function was deemed satisfactory
36	The patient was discharged from the PICU to a high-dependency bed on the paediatric burns ward. She was awake and free from pain, being maintained on methadone 6 mg orally tds and chloral hydrate 500 mg orally at night

Discussion

The most commonly identified goals of sedation in the paediatric intensive care unit are reduced patient distress, fewer unplanned extubations and facilitation of mechanical ventilation.[1] Optimal sedation of paediatric patients is considered difficult despite the use of frequent doses of many sedative agents.[1] Midazolam infusion has been shown to be an effective component in the sedation of the paediatric patient.[2–4] A significant disadvantage of the use of midazolam is the development of acute tolerance,[3] and it has been shown that there is increased clearance during continuous infusion.[4] Opioids are used for both their sedative and analgesic effects. It is well recognized that prolonged or frequent use of opioids is associated with the phenomenon of tolerance. Nevertheless, tolerance to opioids remains largely unexplained despite extensive interest in the underlying mechanism. Some factors are, however, evident; receptor occupancy is necessary for the development of tolerance,[5] both the mu and kappa receptors are affected,[6 7] continuous infusion of opioids produces more rapid tolerance than intermittent administration[8] and morphine tolerance develops without concurrent receptor downregulation.[9]Recent evidence suggests that mechanisms common to other forms of neuronal plasticity may mediate morphine tolerance.[10] Spinal cord *N*-methyl-D-aspartate receptor activation,[11–12] subsequent protein kinase C translocation and activation,[13] and nitric oxide synthesis[12] may be involved. Additionally, altered metabolism of morphine leading to an increased ratio of morphine-3-glucuronide to morphine-6-glucuronide has been associated with uncontrolled nociceptive pain.[14] Interestingly, there appears to be significant similarities between the mechanisms of hyperalgesia and morphine tolerance.[10]

In our patients with established morphine tolerance, with increasing doses of midazolam and additional sedative adjuvants being necessary, it was proposed that another opioid be given in place of morphine. Methadone was chosen for several reasons; it had been reported previously to be an effective analgesic in opioid-tolerant patients,[15–18] it had been used successfully in treating iatrogenic opioid dependency in PICU patients,[19] it is known to be an effective analgesic after paediatric surgery[20] and it produces more prolonged respiratory depression in children than morphine.[21]

In both patients, initial methadone administration produced rapid control of sedation. In patient No. 1, the need for sedative polypharmacy was reduced significantly and adequate sedation and analgesia were maintained at a considerably lower dose-equivalent with respect to morphine. An i.v. loading dose followed by i.v. infusion at the rate described did not produce haemodynamic instability. At discontinuation of the i.v. infusion, a thrice daily i.v. regimen was introduced. With the reduction in dosage of, or withdrawal of, other sedative agents, the daily dose of methadone administered was conservatively reduced. In patient No. 2, methadone was introduced as an initial twice daily bolus regimen on ceasing the i.v. infusion of morphine. Again, there was a considerably lowered dose-equivalent with respect to morphine. After tracheal extubation, methadone administration was changed from the i.v. to the enteral route. The existing daily dose of methadone was increased for two reasons: first, because of the simultaneous reduction in the daily dose of chloral hydrate and second, to make allowance for the fact that the oral bioavailability of methadone is reported to be 81%.[22] In both patients, the relatively long duration of action of methadone permitted twice or thrice daily dosing schedules.

Why can methadone be used successfully in the morphine-tolerant patient?

There is little doubt that there is incomplete cross-tolerance between morphine and methadone in animal models[23 24] and in the human population.[16 17] In the animal model, selective tolerance can be induced by selective agonists for all opioid receptor subtypes without any cross-tolerance occurring between the different receptor subtypes.[25] Methadone is a racemic mixture of laevorotatory (R–) and dextrorotatory (S–) isomers, with the analgesic activity of the racemate being a result almost entirely of the content of the R–isomer.[26] There is stereospecific binding of methadone at the mu-1, mu-2 and delta receptors, with R–methadone having approximately 10-fold higher affinity than S–methadone.[26] Compared with morphine, R–methadone has approximately the same affinity for the mu-1, mu-2 and delta receptors, but has significantly lower affinity than morphine for the kappa receptor. However, methadone has higher intrinsic activity than morphine at the mu receptor.[27]

In animal experiments, it has been demonstrated that the intrinsic activity of opioid agonists is inversely related to the degree of tolerance after continuous infusion.[28] Further work has shown that after establishing morphine tolerance, the potency of morphine is diminished whereas that of methadone is unaffected.[29] Thus the higher intrinsic activity of methadone compared with that of morphine is likely to be a key factor in incomplete opioid cross-tolerance.

Methadone has a chemical structure unrelated to that of morphine; methadone is a diphenylpropylamine whereas morphine is a phenanthrene. As a consequence of its structure, methadone inhibits 5-hydroxytryptamine (5-HT) and norepinephrine uptake whereas morphine does not, and it has been proposed that activity at the mu receptor and inhibition of both 5-HT and norepinephrine uptake combine to enhance the analgesic activity of compounds possessing these properties.[30]

Morphine is metabolized to morphine-3-glucuronide and morphine-6-glucuronide; there is evidence that abnormal accumulation of M-3-G is associated with an antinociceptive effect.[15 31] The metabolites of methadone are pharmacologically inactive.[32] It must be noted that at discontinuation of i.v. morphine infusion in patient No. 1, the ratios of M-3-G to M-6-G and morphine were within the usual ratios compared with previously published paediatric pharmacokinetic data.[33]

In opioid receptor pharmacology, it is considered that the kappa receptor mediates the inherent sedative properties of the opioid group of drugs.[34] It has been noted previously that morphine has a significantly greater affinity for the kappa receptor than either methadone isomer,[26] thus methadone has a markedly lesser inherent sedative action than morphine. Nevertheless, it has been reported that, in animal models where morphine tolerance has been induced, there is substantial tolerance to the pure kappa agonist U-50,488H[6]; thus both mu and kappa receptor activities are altered in morphine tolerance. It is possible that methadone could restore agonist activity at the kappa receptor in morphine tolerance but it must be remembered that methadone has a low affinity for this receptor and any clinical effect under such circumstances is likely to be of little significance.

It appears that, under the circumstances of this case report, it was the restoration of analgesia with methadone that was the essential component of success in restoring sedation in morphine-tolerant patients. This correlates well with the postulate that hyperalgesia and morphine tolerance are associated.

When substituting methadone for morphine in the morphine-tolerant patient, the estimated dose of methadone to be administered must be made cautiously and on an individual basis.[16] For the two patients described, and in previously reported paediatric oncology patients with morphine tolerance,[16 17] it is noteworthy that after introduction of methadone, analgesia was maintained with significantly lower doses compared with those of morphine at the time of its termination.

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HISTORICAL ARTICLE

Anaesthesia in the 1920s

P. M. E. DRURY

Numbers and status of anaesthetists

At the time of publication of the first issue of the *British Journal of Anaesthesia* in July 1923, there were not many whole-time anaesthetists in this country, and these were confined to university teaching hospitals. Blomfield (1922)[5] stated that there were 27 specialists at 12 teaching hospitals in London, and a similar situation existed in the provinces. In the peripheral hospitals, anaesthesia was administered by general practitioners with part-time contracts and a special interest in the subject.[42] But in many cases, emergencies devolved to house officers with very little experience. Woolmer, the first Professor of the Faculty of Anaesthetists, has described his first administration of an anaesthetic (open drop chloroform) in an x-ray department in the dark, given within 1 h of arriving to take up a new appointment.[75] Any medical practitioner was considered competent to give an anaesthetic on qualification, a situation which concerned Buxton.[9] The General Medical Council had required, since 1911, that every doctor, on qualification, should provide evidence of instruction in anaesthesia, but Buxton felt that only the minimum was being done to comply with this requirement. Undoubtedly, many anaesthetics were given by an occasional administrator in a domestic setting or in a surgery. General anaesthesia was also required in the dental chair and many anaesthetics were given by dentists. The Dentists Act of 1921 admitted a few hundred experienced but unqualified people to the Dental Register.

A particular feature of the history of anaesthesia in this country is that, since its earliest days it has been largely in the hands of the medical profession, a fact admired by colleagues in the USA and Europe.[57] In many parts of the USA it was considered to be a nurse's job. No doubt in places the service was excellent but in the 1920s the situation was evolving and, on both sides of the Atlantic, extremely able doctors were emerging who considered anaesthesia to be worthy of a physician's full time attention. This process was postponed in Europe, where surgeons continued to dominate the management of anaesthesia by employing junior assistants, and making widespread use of local and regional techniques.

One reason why specialist anaesthetists were not a common feature was financial. At teaching hospitals, a small payment was usually made in recognition of duties towards undergraduates,[5] but the tradition was that services were given free in return for the opportunity of private practice through contact with surgeons. The anaesthetist, however, did not submit an account, but had to rely on the discretion of the surgeon for payment, generally a small fraction of his fee.[32] Unless there were other sources of income, this could have led to some financial difficulties, and in one case may have been a factor in a suicide.

The perception of today's anaesthetist by patients is not well defined, and it was probably even less so 75 yr ago. On one occasion the public may have been more aware of the anaesthetist's role; in December 1928, King George V had a rib resected for empyema complicating lobar pneumonia.[19] The anaesthetist was Francis Shipway of Guy's Hospital, and when honours were distributed to the medical and nursing team in the following February, he received a knighthood.

Anaesthetic agents

The most commonly used agents in the 1920s were nitrous oxide, ether and chloroform.

NITROUS OXIDE

Nitrous oxide, oxygen and ether had been a popular sequence since the time of Clover, and nitrous oxide and oxygen were often given to accompany local or regional blocks. Other uses of nitrous oxide as the sole agent were inevitably accompanied by hypoxaemia. The technique described by Hewitt in 1893[35] where induction was with 100% nitrous oxide, and a small percentage of oxygen (usually less than 10%) was then added, was widely used for brief operations and in the dental chair. The patient was invariably cyanosed and sometimes jactitated.

McKesson described his secondary saturation technique in 1920[52] and modified it in 1926; 100% nitrous oxide was given first (primary saturation), oxygen under pressure was added to improve the patient's colour, followed by more nitrous oxide (secondary saturation) and oxygen alternately. The technique was condemned by Gwathmey, and Boyle said that it frightened him.[35] It was defended by Sykes, who thought the results were good in McKesson's hands.[71]

Nunn has commented on the apparent acquiescence of the 19th century anaesthetists in hypoxaemia[60] and this continued until well into the

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present century. Nevertheless, nitrous oxide was regarded as a safe anaesthetic, with few attributable deaths. Smith has suggested that the body can tolerate a brief period of acute hypoxaemia, but has speculated on the intellectual cost.

In 1926, the anaesthetic section of the Royal Society of Medicine[50] discussed the purity of the gas in cylinders of nitrous oxide at some length, and agreed that 95% was acceptable. At this time cylinders were not pin-indexed or colour coded. In 1930 a five theatre block with piped gases was opened at St Bartholomew's Hospital in London.[34]

ETHER

Despite manifest disadvantages, ether owed its continuing use in this decade and beyond to the maintenance of circulatory stability at high inspired concentrations, and to its ability, also at high concentrations, to produce abdominal relaxation, which approached that provided by today's relaxants. In these respects it had no real rivals. But it was flammable and explosive, and its after effects were extremely unpleasant. They were vividly described by Henderson and Coburn[33] in the following terms: "patients.... were flaccid, cyanotic, pallid, or grey, with empty veins, weak peripheral pulses, and depressed respiration; it was one to three hours before consciousness returned, and this was followed by nausea, vomiting, and retching for some time afterwards".

CHLOROFORM

Controversy continued to surround this agent. The opinion that "chloroform should be discarded" may well have been expressed in the 1920s; in fact the quotation is from the 19th century. The American Medical Association sought a ban in 1912. In 1923 a "famous" London hospital had 42 chloroform fatalities in 8 weeks, and a correspondent to the *British Medical Journal* regretted that "week after week the chloroform holocaust goes on".[55]

In 1922, Levy published his monograph, *Chloroform Anaesthesia*[41] in which he identified a previously unrecognized cause of death, that of ventricular fibrillation in light anaesthesia, which could also be precipitated by the use of epinephrine. He and others who recognized the hazards gave rules for safe administration, but there were enthusiasts who claimed never to have had any problems. Chloroform was cheap, easy to administer and not explosive. This enigmatic agent was still attracting contributions to the literature in the 1970s.[63]

OTHER INHALATION AGENTS

Ethyl chloride was well established and *di-vinyl ether* appeared at the end of the decade. Both were suitable for brief administrations but were too toxic for more prolonged use.

Acetylene (1922) and *ethylene* (1923) were greeted initially with some optimism because they could be used as the sole agent with an adequate concentration of oxygen, but they had an unpleasant garlic-like odour, were explosive and showed no clear advantage in terms of postoperative nausea and vomiting. They never really became established in the UK.

Cyclopropane became more widely used in the 1930s, but made its first appearance in the literature in 1929. The second human guineapig to receive it was none other than the Nobel laureate Frederick Banting. It was possibly the first agent the cost of which caused some surprise.

The curious episode of *ethanesal* should be mentioned. Boyle and Hewer wrote favourably of this agent,[6] which was ether containing ethylene, carbon dioxide and "potent ketones". There was an erroneous belief that pure ether was not an anaesthetic but merely acted as a solvent for more potent substances. Following unfavourable comments by the American Medical Association and thorough testing by Dale, Hadfield and King[15], ethanesal passed quickly out of use.

NEUROMUSCULAR BLOCKING AGENTS

De Caux used an aqueous solution of curare i.v. in seven patients at the North Middlesex Hospital in 1928. Nothing was published at the time, but Goldman recalled discussing the cases with de Caux and referred to them in a book in 1948.[74] It seems to have been an isolated occurrence.

Techniques and equipment

OPEN METHODS

The technique most commonly used in this decade was still the open drop method[56]; ether and chloroform were given in this way. The liquid was poured from a bottle with a dropper onto gauze held in a wire-framed mask. The face and eyes were protected with material such as gamgee. The liquid had a tendency to freeze on the gauze, reducing the evaporating surface and requiring a change from time to time. Mixtures of chloroform and ether were also given by this method, the most popular being two parts chloroform and three parts ether (C_2E_3) or alcohol, chloroform and ether (ACE) in the ratio 1:2:3. The evidence that they modified the disadvantages of ether or made chloroform safer is not convincing.

BOYLE'S MACHINE

Boyle's machine first appeared in 1917 and was presented to the anaesthetic section of the Royal Society of Medicine in 1918. In its original form it consisted of nitrous oxide and oxygen cylinders, a water sight feed bottle for indicating gas flows and an ether vaporizing bottle, all mounted on a platform with wheels. The cylinders had reducing valves, but because the nitrous oxide was not dry they had a tendency to freeze, and a spirit lamp was provided to keep them warm. The gases were admitted to the ether bottle by a tap. This design underwent modifications so that by 1930 there was a second vaporizing bottle (for chloroform), a third water sight feed tube (for carbon dioxide) and a plunger device on the vaporizing bottle. Boyle readily acknowledged the influence of Gwathmey in his design; a Gwathmey machine was shipped to England in 1916 and used by Boyle as a model.[31]

Boyle's machine did not immediately displace all others; there is evidence that some older equipment continued in use for some time.[25] Magill, in his early communications, recommended Shipway's apparatus. Some anaesthetists had machines to their own design. J. Ross McKenzie of Aberdeen persuaded Coxeter to make a machine for him that would give nitrous oxide, oxygen, carbon dioxide, ethylene, propylene and acetylene.[51]

Another important machine, involving a new principle and to prove of lasting worth in the field of dental anaesthesia and self-administration, was the intermittent flow apparatus shown by McKesson at the British Medical Association meeting in 1926.[54]

INTRATRACHEAL ANAESTHESIA

In 1965, Armstrong Davidson wrote,[16] "Intubation was the most important advance in technique since the introduction of anaesthesia". Although not the first description of tracheal intubation, Rowbotham and Magill's account in 1921 of their solution to the problems posed by the patients at Gillies' Plastic Surgery Unit at Sidcup, Kent, is regarded as the origin of today's routine practice.[66] Mask techniques were not applicable as the majority of operations were on the face. Nitrous oxide, oxygen and ether were insufflated via an intratracheal catheter, but an expiratory tube was also provided. Initially this was a nasopharyngeal tube; later, a second intratracheal catheter was used, and finally a single wide bore red rubber tube.[44]

The tubes were passed using a direct vision laryngoscope. The design was not specified, but Magill did invent his own based on Chevalier Jackson's straight bladed instrument. Rowbotham performed a blind nasal intubation in 1920, and Magill by his description in 1930, hoped that the technique would become more widely used.[45] He was not in favour of routine intubation because he believed that anaesthetists should be skilled in maintaining an airway.

Intratracheal anaesthesia was not at first universally accepted, and there were those who were concerned about ill effects, including surgeons. Hewer recorded the deception of covering the intratracheal tube with a mask. The addition of an inflatable cuff to wide bore tubes was described not by Magill but by Guedel and Waters.[28] Magill and Rowbotham used throat packs where aspiration was a risk.

I.V. AGENTS

The days of the ultra-short acting barbiturates were yet to came, but the first description of the use of barbiturates i.v. was in the 1920s; a considerable amount of literature came from Europe.[1] An early British publication was that of McDonald in 1926.[48] He gave an account of the use of somniferine as a basal hypnotic before abdominal surgery, performed under regional block combined with light general anaesthesia. Lundy (who was largely responsible for furthering the cause of thiopental) used pentobarbital i.v. at the Mayo Clinic.[43] He defined four stages from sedation to very deep unconsciousness, where some surgery was possible, but it was accompanied by severe hypotension, respiratory depression and the need to maintain an airway. The lengthy period of recovery running into hours was no surprise to those familiar with ether anaesthesia. Lundy also mentioned the successful treatment of convulsions with this drug.

Constantin (1929)[14] gave details of a technique using 96% ethyl alcohol in glucose i.v. as the sole agent for abdominal surgery. Surprisingly, expected side effects of headache, nausea and vomiting were not mentioned. This increasing interest of anaesthetists in i.v. agents implied that, for the first time, they came to be regarded as experts at venepuncture.[11]

RECTAL ADMINISTRATION

As with i.v. agents, the initiatives for rectal administration came from outside Britain. Gwathmey was an enthusiast for rectal administration of oil/ether.[29] Blomfield felt that the rectal route was useful "in certain circumstances". Rowbotham felt that basal narcosis with rectal barbiturates was a considerate way to treat children.[65] The discovery of Avertin (bromethol) in 1929 led to its increased use in general surgery and obstetrics, but not as the sole agent.[13]

LOCAL AND REGIONAL ANALGESIA

The majority of techniques in use today were in place in the 1920s. Labat's very comprehensive textbook was published in 1923.[38] Labat was an anaesthetist, and anaesthetic texts always carried a section on local and regional analgesia, but a considerable number of blocks were performed by surgeons, and the extent of anaesthetists' involvement is not always clear. Lee's article on Barker[40] suggests that this pioneer of spinal anaesthesia believed that the technique fell within the province of surgeons. On the other hand, Whitehouse felt that surgeons were trespassing in the anaesthetic field.[72]

Spinal anaesthesia had been used for operations on the head and neck, but a common view held at this time was that they were most useful in operations below the umbilicus.[22 34] The range of suggestions for use is wide, and includes abdominal emergencies such as intestinal obstruction, where its use is less likely today. Spinal anaesthesia was also suggested for the treatment of ileus.[70]

The local anaesthetic drugs used were commonly procaine, the withdrawn CSF being used to dissolve the crystals, and stovaine. Cocaine was by now confined to surface analgesia. Cinchocaine appeared in 1929.[37] Discussions about light and heavy preparations and positioning the patient seem less relevant today. The significance of using small bore needles was recognized.[62] Neurological complications undoubtedly occurred, but were not given great prominence.

The usual approach to the extradural space in this decade was via the sacral route. It was not realized until later that Pages, a surgeon in Madrid, had published an article in 1921 in which lumbar, thoracic and cervical approaches were mentioned. When Dogliotti of Turin described lumbar extradurals in 1931, he was not aware of Pages' work, but later acknowledged it.

Surgery

ABDOMEN

The surgeons of the 1920s would have welcomed the degree of relaxation of the abdominal wall which is now an everyday occurrence; it was often a struggle to close the abdomen. Comparable conditions could be produced by spinal anaesthesia, and also by paravertebral, intercostal or rectus sheath block, supported by coeliac axis block, but occasionally a covering light general anaesthetic was given because of patchy analgesia, or a spinal block that was not high enough. Hewer recommended the insufflation technique used in thoracic anaesthesia (see below), but statements that agents such as ethylene or chloroform produced reasonable relaxation somehow lacked conviction. When McKesson discussed his secondary saturation technique at the Royal Society of Medicine in 1926, it was felt by some speakers that the degree of muscle rigidity would not be accepted by English surgeons.[53]

BALANCED ANAESTHESIA

Crile was a strong advocate of a combination of local and light general anaesthesia with nitrous oxide (anoci-association). He argued that if all afferent stimuli including fear were abolished the patient would not suffer shock and its consequences. Although his work is much quoted, it is difficult to know to what extent his ideas were put into practice. One author thought that lip service was paid to them while people continued to pour quantities of ether and chloroform on to masks. Even in Europe where these methods were commoner, it was felt that Crile's work was not as well known as it should have been.[23]

Although many routine surgical procedures are unchanged, our predecessors in the 1920s faced many problems that do not exist today.

THORAX

Surgery was an important part of the treatment of tuberculosis, using such procedures as rib resection for empyema and thoracoplasty, which could be quite extensive, for reducing the size of cavities. Lobectomy was on the increase towards the end of the decade,[18] but pneumonectomy was not yet established. Chest wall procedures could be carried out satisfactorily under local anaesthesia. Other procedures were performed with combinations of local anaesthesia, sedation, narcosis and general anaesthesia which varied from centre to centre. As there were no antibiotics, and spread of the disease within the lung was feared where sputum was plentiful, there was a demand for a plane of anaesthesia which preserved the cough reflex, an exacting requirement in the days before one-lung anaesthesia, double-lumen tubes and bronchus blockers.

The usual solution to the pneumothorax problem was intratracheal insufflation of nitrous oxide, oxygen and a volatile agent, usually ether, under sufficient pressure (10–20 cm H_2O) to maintain some expansion of the lungs. Respiratory movements were much diminished or even absent, yet oxygenation remained good through diffusion. Periodic deflation of the lungs was necessary to maintain venous return. The technique was developed clinically in America by Elsberg.[21]

THYROID SURGERY

Many patients with florid Graves disease presented for thyroidectomy, as there was no effective medical treatment for thyrotoxicosis. There were no consistent recommendations for anaesthetic management, but it seemed widely agreed that chloroform was contraindicated. Crile believed that these highly nervous and excitable patients should not be told the day of their operation. They were given practice inhalations and injections of sterile water for a few days. On the appointed day, nitrous oxide, morphine and hyoscine were administered to the patient in bed; transfer took place to the operating theatre and the operation was completed with local anaesthetic supplement. This method was known as "stealing the thyroid".

OBSTETRICS

In operative obstetrics, all available anaesthetic techniques were used. There did not seem to be any awareness of the risk of regurgitation and inhalation of gastric contents.

CARDIAC SURGERY

There was occasional discussion in the journals on the role of surgery in valvular heart disease.[59] Souttar performed a transauricular split of the mitral valve at the London Hospital in 1929.[20] The anaesthetic was administered by Lindsay, a surgical colleague, using open drop ACE mixture at induction and intratracheal nitrous oxide, oxygen and ether by insufflation.

The perioperative period

PREPARATION

The statement that preoperative purgatives and enemas should be phased out[2] suggests that the practice was continuing in some quarters. On the other hand, there was encouragement to give adequate fluid up to the time of operation, although the route of administration was not specified.

PREMEDICATION[67 68]

Although the word may have been used informally, the first mention of it in print seems to be by McMechan in 1920. Previously, terms such as preliminary medication or pre-anaesthetic medication were used. The drugs available were atropine, morphine and hyoscine. It is surprising how little those drugs were used preoperatively in this country before 1911, when there was increased interest in their properties. Sometimes they were all given together, and although respiratory depression prolonged induction with ether, it also made it smoother. But despite reduction of apprehension, some surgeons and anaesthetists were unhappy about the use of both morphine before operation, especially before chloroform, and of hyoscine, which was thought to contribute to increased muscular rigidity.

Atropine was the only drug which could be said to have been prescribed routinely, particularly for its effect in reducing the considerable bronchorrhoea stimulated by ether. It was also advocated before the administration of chloroform as protection for the heart, particularly against vagal overactivity. There is some doubt surrounding this proposition, and as Levy pointed out, the use of atropine did not prevent chloroform deaths.[41]

The term "twilight sleep" was given to the practice of injecting morphine and hyoscine in generous doses in the labour ward, with additional doses of hyoscine to produce amnesia. The price of this was an increased degree of restlessness.

RISK ESTIMATION

There was no ASA classification or Goldman multifactorial risk index, but there were some attempts to assess preoperative cardiac status. Goodall believed that every general hospital should have a cardiac department where routine preoperative examination of surgical patients could be done.[26] Blomfield emphasized the significance of dyspnoea as a symptom, and believed that information from exercise testing and breath-holding was important. Moots[59] proposed some quantitive tests, such as the pressure ratio (pulse pressure/diastolic pressure, range 30–70%) and the energy index (the product of the sum of systolic and diastolic pressures, and heart rate; range 12–18 000), which is similar to the more recent concept of rate–pressure product.

MONITORING

Much monitoring must have been rudimentary. With two hands occupied holding a face mask, or pouring liquid on to gauze, visual assessment of respiration and colour would have been the main observations, with occasional palpation of the pulse and examination of the pupils. Guedel's signs had been published in 1920.[27] Recent studies have demonstrated that detection of cyanosis is not always reliable,[12], even by experienced observers, so that some degree of hypoxaemia must have been common, especially in patients breathing air.

From the standpoint of the 1920s, the recording of arterial pressure was relatively new. Hewer considered that it should be recorded every 5 min during abdominal surgery and recorded on a graph.[34] He used a brachial artery stethoscope and a cuff. Mennell, of St Thomas', who worked with the eminent neurosurgeon Sir Victor Horsley, also emphasized the important of frequent readings.[58] Investigations were beginning into the indirect measurement of venous pressure in relation to anaesthesia.

RESUSCITATION

In an era when techniques of cardiopulmonary resuscitation are widely taught, it might be thought that our predecessors were not so skilled in this area. Information was rather scattered in various texts, and as a considerable number of anaesthetists were self-taught, it would be a matter of chance whether the necessary knowledge was to hand. Nevertheless, there were some effective techniques for the treatment of respiratory and circulatory failure.

Various methods of artificial respiration, such as the Silvester, had been described from the 1850s. Compression of the chest is also described,[8] so that some patients may have unwittingly received external cardiac massage. Mouth-to-mouth respiration is mentioned by Levy and others as a little known technique which deserved a wider awareness.[41] If an intratracheal catheter was in place it could be used for insufflation; it could also be blown down, or attached to a pump or bellows (perflation). It does not seem to have occurred to anybody to squeeze a rebreathing bag.

Internal cardiac massage was in the repertoire. If the abdomen was open the heart was approached through the diaphragm, otherwise an intercostal incision was made. Intracardiac epinephrine was also used. Although these methods were undoubtedly effective in some cases, there are no values for success rates.

Treatment of hypovolaemic shock was less confident. The feasibility of blood storage[64] and person to person transfusion had been demonstrated during World War I, but there were no blood banks, and registration of donors was only just beginning. There was a reluctance to use the i.v. route except as a last resort,[69] despite wartime experience with gum solution as a plasma expander.[3]

Stimulant drugs such as strychnine had been in use for some time. Ephedrine was introduced in 1924.

POSTOPERATIVE CARE

The treatment of postoperative pain has a low profile in the literature of this period. Because of more prolonged recovery from anaesthesia, it did not require the early attention that it does today, but presumably patients were handed over to nursing staff and given morphine i.m. One thoracic surgeon prescribed morphine for his patients for 12 days. The rectal route was sometimes used for administering analgesia combined with sedation, for example aspirin and bromide. Maintenance fluids were seldom given i.v., but more usually by the rectal route or subcutaneously.

More thought was given to the problem of postoperative vomiting, although treatment was empirical. There were no specific antiemetic drugs; atropine and hyoscine had antiemetic properties but were used for other reasons. A variety of hot and cold liquids, medicinal, mineral waters, beverages and also alcoholic drinks such as brandy and champagne had their advocates. It had to be borne in mind that not all postoperative vomiting was related to the anaesthetic; the cause was sometimes surgical. It was hoped that the use of warmed intratracheal ether, and also Henderson's de-etherization technique with carbon dioxide,[33] would reduce the incidence of vomiting. The possibility of recovery wards was raised by Flemming,[24] but he was concerned that surgeons voracious for beds would seize them.

Insulin, of which limited supplies started appearing in 1923, was becoming more widely available.

COMPLICATIONS

The Section of Anaesthetics at the Royal Society of Medicine discussed deaths in April 1923.[10] Mennell was able to assure them that every death during anaesthesia at St Thomas' was investigated by a subcommittee consisting of an anaesthetist, pathologist and a surgeon. Many cases were unrelated to anaesthesia, but in some it played a principal part. Flemming pointed out that the death rate associated with operation was stationary, despite an increase in the number of administrations. It is to be hoped that the report of three deaths in one day at Poplar Hospital, which was the subject of a question in parliament,[36] was an aberration, although it suggests incompetence.

Some members were concerned that it was a statutory requirement to report on deaths on the table to the coroner, who then usually held an inquest. There was unhappiness about the quality of newspaper reporting, and the fact that these deaths were classified by the Registrar General as anaesthetic deaths. There was no requirement to report postoperative deaths (some of which might have been associated with anaesthesia).

Post mortem was generally unhelpful where there was no gross pathology, fatty degeneration of the heart being a useful label. Status lymphaticus,[7] a syndrome characterized in young people by lymphoid hyperplasia, was a recurring diagnosis, although it later lost its validity. In a retrospective review, McIntosh[49] considered that this diagnosis obscured the fact that death was caused (then as now) by failure to maintain an airway. He also demonstrated that coroners were frequently lenient in finding no fault with the treatment. There was a reminder that death could also occur with local anaesthesia.[47] Mayer described 46 cases in 1924, 26 caused by cocaine.

Pinson[61] estimated in 1930 that there were at least 100 fires and explosions annually in theatre. Many of these resulted in injuries of a minor nature, but there were some deaths. The increasing use of diathermy, for coagulation and debulking of tumours, was an additional risk factor.

In the first issue of *Current Researches in Anesthesia and Analgesia*, an editorial by McMechan implied that the death of a Dr Curtain was associated with the administration of 30 000 ether anaesthetics. The author regretted that medical science provided no protection from this, whereas it did provide for the protection of radiologists.

Literature and postgraduate activity

BOOKS

McIntosh is quoted as saying at this time that the only means of acquiring knowledge beyond the basics was to study books published abroad.[4] Presumably he was referring to Gwathmey's book,[29] the second edition of which was published in 1925. Two well established British books appeared in new editions; a sixth edition of Buxton's book of 1888 appeared in 1920[8] and a fifth edition of Hewitt's book of 1893[35] was published in 1922. Hewitt died in 1916 but the new editor, Robinson, kept the name. Blomfield produced a fairly substantial book of 424 pages in 1922,[5] which was well reviewed in the *British Medical Journal*, but as Zuck[76] has pointed out, there was no major British specialist textbook published between 1922 and 1947. Other influential names did not enter the field until the 1930s (Guedel, Lundy, Minnitt, Waters). Some surgical books contained a chapter written by an anaesthetist (e.g. Magill[46]).

JOURNALS

The first issue of *Current Researches in Anesthesia and Analgesia* appeared in 1922; it was a continuation of the proceedings published by the National Anesthesia Research Society Inc. It was edited by McMechan, who had also been responsible for the twice yearly anaesthesia supplement in the *American Journal of Surgery*, which had started in 1914. Once *Current Researches* became established, these supplements were phased out.

The *British Journal of Anaesthesia* was a new venture for the UK, although with a target of 500 subscribers it was looking for international recognition. The price was 10s 6d for a single issue and the editor pronounced himself satisfied with progress at the end of the first year. It was his ambition to publish the journal monthly.

An earlier source of printed material was the anaesthetic section of the Royal Society of Medicine, which was published in the proceedings, and which had been formed in 1908 with more than 100 members.

It should be acknowledged that the general medical journals, the *British Medical Journal* and the *Lancet*, and the *Journal of the American Medical Association* were reasonably generous in providing space for matters of interest to anaesthetists. Some of it took the form of abstracts and reports of meetings, but there was also representation in articles, editorials, book reviews and correspondence.

SOCIETY MEETINGS

The British Medical Association Annual Scientific Meeting had an anaesthetic section from 1920. In 1925, A. R. Cox, the secretary of the British Medical Association, met McMechan at an international congress and invited him to the next meeting in Nottingham. This was the first time that associations from Britain and North America had met and it cemented transatlantic friendships that had begun in World War I. McMechan was later elected honorary associate editor of the *British Journal of Anaesthesia*.

There was a Scottish Society of Anaesthetists formed by a group of general practitioners in 1914. The first provincial society in England was the Liverpool Society of Anaesthetists (1930). Anaesthetists did of course give papers to local medical societies.[36]

ANAESTHETIC DEPARTMENTS

In 1927, the Dean of a new medical school at the University of Wisconsin approached some of his contemporaries with a view to setting up university departments; among them was Ralph M. Waters. He is quoted as saying[73] that the formation of the specialty depended "first upon men, second upon publications, and third upon organisations through which men meet for mutual development by exchange of ideas". The reputation of his department grew steadily, and it attracted visitors from all over the world. Among them was McIntosh, the holder of the first British chair at Oxford, who later paid a very warm tribute to Waters.[50]

Another significant appointment at this time was that of J. S. Lundy at the Mayo Clinic. In addition to his work on i.v. agents, he developed an anatomy laboratory.[17]

FUTURE ASPIRATIONS

In the first issue of the *British Journal of Anaesthesia*, the editor had a wide ranging view of the future of the specialty, although the reality had to wait until the formation of the Association of Anaesthetists in 1932. Cohen returned to the subject in an editorial in January 1927, starting with the premise that the present state of anaesthetic instruction was not worthy of such an important branch of surgery. "Nothing less than a well-equipped Department or School, with paid instructors capable of teaching all the various types of general and regional anaesthesia, as well as Physiology, Chemistry, and the Mechanics of the Subject will suffice".

The president elect of the British Medical Association, Sir Robert Philip, who had for a time acted as an anaesthetist for Thomas Keith of Edinburgh, a pioneer of ovariotomy, addressed the Section of Anaesthesia at the 1926 Scientific Meeting, and said that the satisfactory practice of anaesthesia rested ultimately in physiology. The anaesthetist would be a physician in the best sense of the word.

The anonymous obituarist of H. W. Webber (1955) thought that 1922 was a year when widening knowledge had begun to stir the rather static world of anaesthesia. The stage was now set for further advances in the 1930s.

Conclusion

Although anaesthesia was still crude in some ways, the 1920s saw many developments. The wider use of tracheal intubation, introduction of anaesthetic machines and appearance of new journals are some examples that have been mentioned above. More doctors were becoming interested in anaesthesia as a specialty, and there was movement towards a wider role beyond mere administration of gases. The appearance of the first recognized department of anaesthesia devoted to teaching and research was an important pointer for the future.

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CITATION CLASSIC

Commentary

Prys-Roberts C, Greene LT, Meloche R, Foëx P. Studies of anaesthesia in relation to hypertension. II: Haemodynamic consequences of induction and endotracheal intubation. *British Journal of Anaesthesia* 1971; **43**: 531–547.

This frequently cited article by Prys-Roberts and colleagues is one of a series by this group of investigators in the early 1970s that assessed the effects of anaesthesia, tracheal intubation and ventilation in treated and untreated hypertensive patients compared with normotensive patients.[1 2] The article that I will comment on examined specifically the haemodynamic response to induction of anaesthesia, and subsequent laryngoscopy and tracheal intubation in treated and untreated hypertensive patients. As I discuss the content and clinical implications of this investigation, it will become obvious why this article became a citation classic of the *British Journal of Anaesthesia.*

The study was performed in the following way. Arterial pressure, heart rate and the electrocardiogram were monitored continuously in 16 untreated and 20 treated adult (aged 24–72 yr) hypertensive patients during and after induction of anaesthesia, laryngoscopy and tracheal intubation. Anaesthesia was induced with either thiopental 50–200 mg (n = 15), methohexital 80–100 mg (n = 6), propanidid 200–300 mg (n = 4), diazepam 10–20 mg (n = 2) or neuroleptanalgesia (phenoperidine 0.8–1.6 mg, droperidol 5–9 mg, n = 9). After loss of consciousness, patients breathed a mixture of 1% halothane in nitrous oxide 7 litre min^{-1} and oxygen 3 litre min^{-1} for 5–10 min until arterial pressure and heart rate had stabilized (i.e. steady state after induction). Subsequently, succinylcholine 75–100 mg was administered i.v. Approximately 2 min later, laryngoscopy was performed (with the laryngoscope held in position for 15–20 s), the larynx and trachea were sprayed with 4% lignocaine 2 ml, and the trachea intubated. After intubation, the same gas mixture as that used before intubation was used to maintain anaesthesia. Spontaneous respiration was allowed to return and to continue undisturbed until arterial pressure and heart rate had stabilized (i.e. steady state after intubation). Four additional patients underwent blind nasal intubation.

Of the numerous results of this investigation, the most relevant clinically can be summarized as follows. First, in untreated and treated hypertensive patients, induction of anaesthesia and subsequent tracheal intubation were associated with pronounced swings in arterial pressure. Whereas the absolute decrease in arterial pressure after induction of anaesthesia was greater in untreated patients, the incidence of hypertension exceeding conscious control values was higher in the treated patients (70 *vs* 42%).

Second, in the majority of patients, maximum increases in arterial pressure and heart rate occurred during laryngoscopy but before intubation. In contrast with arterial pressure, heart rate increased to values above awake control values in both groups of patients. The increase in heart rate was accompanied by a 40% incidence of arrhythmias which persisted for 2–3 min after intubation. The hyperdynamic cardiovascular response was short lived.

Third, there were no significant cardiovascular changes during blind nasotracheal intubation.

On the basis of these findings the authors concluded that "... hypertensive patients are as much if not more at risk during induction of anaesthesia, and during subsequent laryngoscopy and tracheal intubation, as they are during steady-state anaesthesia". They continued that "... it was surprising to find that patients on anti-hypertensive therapy with well controlled arterial pressures, were equally prone to develop a hypertensive response to intubation ...". These are valid and clinically important conclusions which nevertheless require additional comments to put them into perspective.

By today's standards many of the "treated" hypertensive patients would be categorized as poorly controlled (11 (55%) had diastolic pressures >110 mm Hg and 15 (75%) systolic pressures >160 mm Hg). Eleven patients had pathologically increased diastolic and systolic arterial pressures. Furthermore, the pharmacological approach to the treatment of hypertension has changed entirely in the past 25 yr. Methyldopa, reserpine, guanethidine, bethanidine, cyclopenthiazide and debrisoquine sulphate are no longer or very rarely used. Thus haemodynamic responses to various perioperative stimuli (including induction of anaesthesia, laryngoscopy and intubation) may differ quantitatively and qualitatively.

One might argue that the haemodynamic responses were not so much a function of increased baseline arterial pressures but rather that of the (low) dose of drug used to induce anaesthesia. Measurements during steady-state conditions after induction of anaesthesia were performed at 5–10 min after injection of the induction agents, measurements during laryngoscopy and intubation at 10–15 min, and those during steady-state conditions after intubation approximately 15–25 min after injection of the induction agent. Considering the progressively increasing time intervals between drug injection and measurements it is likely that the observed haemodynamic responses were determined primarily by the continuously breathed gas mixture of 1% halothane and 70% nitrous oxide.

Several other factors may have influenced the results. Most patients were not premedicated. The induction agents were not administered in random order but chronologically. The number of patients in most of the groups was too small to be able to make valid comparisons between drugs or between treated and untreated hypertensive patients. Normotensive patients were not included as controls. The statistical test used to compare data between treated and untreated patients was not mentioned, and the paired t test was used for multiple comparisons.

Despite such limitations, the investigation by Prys-Roberts and colleagues taught us a great deal. We learned that hypertensive patients are prone to greater variations in arterial pressure than normotensives. The excessive swings in arterial pressure associated with the sequence of induction of anaesthesia followed by laryngoscopy and intubation may lead to myocardial ischaemia in the susceptible patient (as indicated in figs 1 and 2 of the article). We learned that laryngoscopy and tracheal intubation are intense stimuli that can evoke a pronounced hyperdynamic cardiovascular response. Although most likely of no clinical consequence to the healthy patient (and probably not even to the patient with stable coronary artery disease because of the short-lived nature of the sympathetic stimulation), this response is potentially life-threatening for patients with symptomatic aortic or cerebral aneurysm, unstable coronary syndromes, recent myocardial infarction or intracranial hypertension.

The clinical implications of the various findings were numerous and continue to influence practice today. The results implied that it might be preferable to postpone elective surgery in the uncontrolled hypertensive patient until good control of arterial pressure has been achieved. Even 25 yr later, however, management of the hypertensive patient is still a matter of ongoing controversy.

The results indicated the importance of attenuating the cardiovascular response to laryngoscopy and tracheal intubation in patients at risk. Although deep levels of anaesthesia effectively and predictably blunt or even abolish the hyperdynamic circulatory response, such an approach may cause pronounced hypotension and bradycardia when the noxious stimulus has ceased, resulting in even greater arterial pressure swings. It might be preferable to attenuate the cardiovascular stimulation by topical anaesthesia, nerve blocks, i.v. lidocaine, α_2 agonists or β adrenoceptor antagonists.

The results clearly implied that the usual rapid-sequence induction of anaesthesia with a short-acting barbiturate followed by succinylcholine (preceded, at most, by a small dose of opioid) provides only minimal protection against the pressor and chronotropic effects of laryngoscopy and tracheal intubation. Limiting the duration of laryngoscopy (in this way minimizing stretching of tissue in the epi- and laryngopharynx) should be an effective preventive measure. Laryngoscopy exceeding 15–30 s seems to progressively stimulate cardiovascular reflexes. In accordance with the authors' findings during blind nasal intubation, fibreoptic nasal intubation blunts or, depending on baseline sedation, almost abolishes the increases in arterial pressure and heart rate during intubation.

No doubt the study by Prys-Roberts and colleagues considerably advanced our knowledge of the perioperative management of the hypertensive patient. It influenced daily anaesthetic practice and, although extremely difficult to quantify, possibly improved patient outcome. No less important, by posing numerous unanswered questions it triggered subsequent work in this area (for example, study on the means of attenuating the cardiovascular response to laryngoscopy and intubation, and on the mechanisms evoking this response). Perhaps most important, the data collected more than 25 yr ago have retained their clinical relevance. It is, therefore, of no surprise that the article by Prys-Roberts and colleagues has become one of the most cited in the history of the *British Journal of Anaesthesia*.

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STUDIES OF ANAESTHESIA IN RELATION TO HYPERTENSION
II: HAEMODYNAMIC CONSEQUENCES OF INDUCTION AND ENDOTRACHEAL INTUBATION

BY

C. Prys-Roberts, L. T. Greene, R. Meloche and P. Foëx

SUMMARY

The electrocardiographic and haemodynamic responses to the induction of anaesthesia, followed by laryngoscopy and endotracheal intubation have been studied in a group of 16 untreated hypertensive patients, and a group of 20 patients receiving antihypertensive therapy up to and including the day of operation. The influence of five different induction agents, thiopentone, methohexitone, propanidid, diazepam, and neuroleptanalgesia induced by a combination of phenoperidine and droperidol were compared. Neuroleptanalgesia caused less arterial hypotension than any of the other agents, but afforded only marginally more protection than other agents against hypertension, tachycardia and dysrhythmia associated with laryngoscopy and tracheal intubation. Both propanidid and diazepam caused dramatic but transient hypotension in a small number of patients and were not investigated further. Unlike its effects in normotensive subjects, methohexitone caused greater hypotension than thiopentone in hypertensive patients. The rationale is presented for the prophylactic blockade of beta-adrenergic receptors to prevent hypertensive crises during laryngoscopy and intubation in both treated and untreated hypertensive patients.

During preliminary studies of the circulatory effects of anaesthesia in treated and untreated hypertensive patients (Prys-Roberts, Meloche and Foëx, 1971) we observed that most of the patients experienced three periods of circulatory instability: during induction, during and after tracheal intubation, and during the immediate period surrounding awakening. Tachycardia and hypertension are well documented complications of laryngoscopy and tracheal intubation in normotensive patients under a variety of anaesthetic techniques (Reid and Brace, 1940; Burstein, Lo Pinto and Newman, 1950; King et al., 1951; Rosner, Newman and Burstein, 1953; Takeshima, Noda and Higaki, 1964; Forbes and Dally, 1970) and during tracheal suction in patients with tracheostomy (Corbett, Kerr and Prys-Roberts, 1969). Dingle (1966) and Forbes and Dally (1970) suggested that the hypertensive response of normal subjects to laryngoscopy and intubation might be enhanced and prove dangerous to hypertensive subjects.

We have compared the haemodynamic effects of five agents for the induction of anaesthesia in treated and untreated hypertensive patients, in the hope of establishing the relative safety of each, and have studied the haemodynamic and electrocardiographic responses of these patients to the subsequent laryngoscopy and tracheal intubation.

CLINICAL MATERIAL AND PROCEDURES

The haemodynamic responses of 36 hypertensive patients were studied during the induction of anaesthesia, and during the sequence of short-term paralysis with suxamethonium followed by laryngoscopy and tracheal intubation. The patients were aged between 24 and 72, and were divided into two groups: those whose hypertension was untreated, and those who had been treated for varying periods of time with antihypertensive drugs, and who were receiving their drugs in the prescribed dosage up to and including the day of operation. Details of the patients are shown in table I.

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TABLE I

Details of patients included in the study, their anti-hypertensive treatment, and haemodynamic values measured during the awake control period. Patients are divided into groups according to the induction agent used.

Patient	Sex	Age	Arterial pressure (mm Hg)	Cardiac output (l./min)	Heart rate	Systemic vascular resistance (units*)	Stroke vol. (ml)	Anti-hypertensive treatment	Premedication
Thiopentone induction									
01	F	63	162/72	6.26	66	1302	95	AMD	Nil
02	M	52	136/76	—	62	—	—	AMD, N–K	Nil
03	M	50	212/120	7.24	78	1667	93	AMD, B, N–K	Nil
09	M	59	147/83	4.73	78	1824	61	AMD, N–K	Nil
13	F	61	128/84	—	105	—	—	B, N–K	Nil
14	F	27	208/112	4.50	46	2557	98	AMD, B, N–K	Nil
15	F	68	178/76	4.27	63	2115	68	Reserpine, tranquillizer	Nil
16	F	69	180/86	3.60	77	2641	47	AMD	Nil
19	F	68	214/90	3.86	85	2836	45	Reserpine	Nil
20	F	47	215/98	5.97	99	1914	60	B, N–K	Nil
04	M	59	200/99	4.90	62	2625	79	Nil	Nil
05	F	72	218/84	4.14	64	2267	65	Nil	Nil
07	M	57	184/103	6.02	72	1752	84	Nil	Nil
10	M	71	229/118	4.78	50	2591	100	Nil	Pa 10, H 0.2
12	M	55	162/82	6.24	64	1359	100	Nil	Pa 20, H 0.4
Neuroleptanalgesia induction									
21	F	70	204/102	4.05	82	2644	49	Nil	Nil
22	F	61	230/116	—	81	—	—	Nil	Nil
25	M	68	232/104	—	54	—	—	B, N–K	Nil
26	F	44	170/92	6.01	67	1444	90	Dbq, N–K, tranquillizer	Nil
27	M	24	196/104	6.56	85	1681	77	Nil	Nil
28	M	44	178/100	4.28	59	2353	73	B, N–K	Nil
29	M	51	165/95	4.66	84	2126	44	Guanethidine	Nil
31	M	51	160/86	6.74	60	1352	110	Reserpine, tranquillizer	Nil
38	F	69	183/88	4.59	75	2176	55	Nil	Nil
Propanidid induction									
32	F	49	288/128	—	54	—	—	Nil	Pa 20, H 0.4
33	F	37	164/88	—	58	—	—	Nil	Pa 20, H 0.4
34	F	51	206/110	—	72	—	—	AMD, N–K	Pt 100, A 0.6
35	F	54	281/143	4.38	99	3631	44	Nil	Pa 20, H 0.4
Methohexitone induction									
40	F	65	195/80	5.59	84	1715	67	Nil	Nil
41	M	46	176/92	—	67	—	—	Nil	Nil
42	F	45	208/112	—	60	—	—	Nil	Nil
43	F	63	175/105	—	100	—	—	Nil	Pa 20, A 0.6
44	M	69	195/80	—	75	—	—	AMD, tranquillizer	Pt 50, A 0.6
45	M	69	200/125	—	115	—	—	AMD, phenobarbitone	Pt 50, A 0.6
Diazepam induction									
36	F	72	190/105	—	92	—	—	AMD, N–K	Nil
37	F	69	160/70	—	75	—	—	AMD, N–K	Nil

Premedication: Dose in mg; Pa=papaveretum; Pt=pethidine; H=hyoscine; A=atropine.

Anti-hypertensive drugs: AMD=methyldopa; B=bethanidine; N–K=Navidrex-K (cyclopenthiazide with slow release potassium chloride); Dbq=debrisoquine sulphate.

*Resistance units: dyne sec cm^{-5}

The patients were interviewed and examined by one of us on the day preceding the study, and their consents to the observations were obtained after a full explanation of the purpose of the studies, and pre-operative assessment as described in full by Prys-Roberts, Meloche and Foëx (1971). Although most of the patients were not premedicated since baseline measurements on the conscious, undepressed, resting patient formed an integral part of the complete studies, some patients were premedicated according to their own or their anaesthetist's wishes.

The patients were brought to the anaesthetic room in their own beds, and lay in a supine position with one pillow throughout the studies. Under local analgesia, an 18-gauge Teflon cannula (Becton-Dickinson Longdwel) was inserted percutaneously into a brachial artery. In some patients, a larger version of the same cannula was inserted into the contralateral basilic vein, and a 90-cm nylon catheter was floated centrally until its tip lay in the right atrium, right ventricle or pulmonary artery. Standard electrocardiographic limb and chest leads were applied.

Arterial pressure was measured with a Statham P37 miniature pressure transducer connected directly to the arterial cannula, and right heart pressures were measured with a Statham PM131 TC transducer. Instantaneous heart rate was measured with a Neilson tachometer (Devices Ltd) triggered by the R wave of the e.c.g. Cardiac output was measured by the dye dilution method, using a Waters XC-302 cuvette densitometer and amplifier to detect and amplify the changing concentration of indocyanine green in arterial blood. All variables were simultaneously recorded on an Elema-Schönander EM 81 ink-jet recorder, and displayed on a four-channel oscilloscope (LAN electronics). Details of the methods were given in the previous communication (Prys-Roberts, Meloche and Foëx, 1971).

The choice of induction agent was determined chronologically; the first 15 patients received thiopentone sodium (2.5 per cent) in sufficient dosage (50–200 mg) to ensure loss of consciousness and acceptance of face-mask administration of the maintenance gas mixture—1 per cent halothane in nitrous oxide (7 l./min) and oxygen (3 l./min). The subsequent 9 patients were induced by neuroleptanalgesia (NLA) produced by incremental doses of phenoperidine (0.1 mg) and droperidol (1.0 mg) given over a period of 5–15 minutes until the patient appeared to be asleep (though responding to command) and accepted an anaesthetic facemask. The range of the accumulated doses of the drugs used to produce NLA were: phenoperidine 0.8–1.6 mg and droperidol 5–9 mg.

Four patients received propanidid (200–300 mg) in a 5 per cent solution, administered through the right heart catheter over a period of 15–20 seconds, followed by facemask administration of the maintenance gas mixture as soon as the hyperventilatory phase had commenced. Two patients were induced with 10–20 mg diazepam given over a period of 30 seconds, followed immediately by maintenance anaesthesia.

The last group of 6 patients received methohexitone (Brietal Sodium) in a dose of 80–100 mg, administered as a 1 per cent solution over a period of 30 seconds.

Prior to the moment of induction, all the patients were allowed to lie undisturbed for about 5 minutes while continuous recordings were made of the electrocardiograph (usually lead II), instantaneous heart rate, arterial pressure and right heart or pulmonary arterial pressures. Measurements of cardiac output were performed in duplicate during this period. The patients were not told when the induction agent would be administered, in the hope that pre-induction apprehension would not cause haemodynamic changes which would obscure the pharmacological effects of the induction agents.

Following the administration of the induction agent, the patients breathed the maintenance gas mixture through a Magill attachment and facemask for 5–10 minutes until arterial pressure and heart rate had stabilized. This stage was designated the post-induction steady-state period (1), and in many patients served also as a pre-intubation control period. In other patients, studies of baroreceptor function were performed during this interval, and a further measurement was made to serve as a pre-intubation control value during steady-state anaesthesia (2).

Endotracheal intubation.

When a steady state of spontaneous ventilation was established, suxamethonium 75–100 mg was administered intravenously, and when the muscle fasciculations appeared gentle manual inflation of

TABLE II

Responses of treated and untreated hypertensive patients to induction of anaesthesia with thiopentone, and the subsequent sequence of muscular paralysis, laryngoscopy and tracheal intubation, and maintenance anaesthesia. Mean values are shown with SD in parentheses.

		TREATED HYPERTENSIVES (n=10)						UNTREATED HYPERTENSIVES (n=5)					
		SAP (mm Hg)	DAP (mm Hg)	MAP (mm Hg)	HR (beats/min)	$\dot{Q}$ (l./min)	SVR (dyne sec cm^{-5})	SAP (mm Hg)	DAP (mm Hg)	MAP (mm Hg)	HR (beats/min)	$\dot{Q}$ (l./min)	SVR (dyne sec cm^{-5})
Awake (control)		178 (34)	90 (16)	121 (21)	76 (18)	5.05 (1.29)	2107 (531)	199 (27)	97 (15)	134 (17)	71 (14)	5.25 (0.94)	2118 (550)
After induction													
1 min		175 (41)	96 (29)	123 (32)	88 (16)	—	—	161 (17)	88 (13)	113 (11)	80 (8)	—	—
3 min		157** (40)	87 (26)	110** (30)	82 (18)	—	—	163 (26)	86 (7)	111 (13)	70 (7)	—	—
Steady-state	(1)	130*** (35)	72** (20)	91*** (22)	68 (13)	3.94** (0.92)	2022 (395)	130* (24)	71* (10)	91* (12)	63 (6)	4.53 (1.10)	1645* (296)
Steady-state	(2)	127 (34)	71 (19)	90 (21)	70 (15)	4.03 (1.13)	1950 (288)	126 (25)	69 (10)	88 (12)	63 (7)	4.08[2]	1868[2]
After suxamethonium		124 (26)	71 (15)	89 (18)	75 (13)	—	—	114 (26)	63 (13)	81 (16)	63 (3)	—	—
After laryngoscopy (maximum values)		177††† (25)	101†† (14)	126†† (17)	96†† (13)	—	—	170†† (34)	95†† (8)	120††† (14)	80 (5)	—	—
Steady-state	(3)	121 (19)	68 (17)	86 (16)	70 (14)	3.74 (0.98)	1838 (320)	109 (16)	58† (12)	74 (12)	58† (7)	3.26[2]	1869[2]

Paired two-tailed t-test:			
comparison of values against awake control	$P<0.05$	*	SAP = systolic arterial pressure
	$P<0.01$	**	DAP = diastolic arterial pressure
	$P<0.001$	***	MAP = mean arterial pressure
comparison of values with steady-state (2)	$P<0.05$	†	HR = heart rate
	$P<0.01$	††	$\dot{Q}$ = cardiac output
	$P<0.001$	†††	SVR = systemic vascular resistance

[2] means based on two measurements only

the lungs was started. It was established in an early group of patients that haemodynamic changes did not occur within the first 30–40 seconds if the lungs were not inflated, and that manual inflation for a period of 1 minute without further interference produced no significant changes from the control values. Laryngoscopy was therefore delayed for 20 seconds after visible fasciculations had ceased, and the laryngoscope (Macintosh) was held in position for optimal visualization of the vocal cords for 15–20 seconds before spraying the larynx and trachea with 2 ml of 4 per cent lignocaine. A cuffed oral endotracheal tube (Oxford pattern), lightly lubricated with lignocaine gel, was inserted and its cuff immediately inflated. Manual inflation of the lungs was maintained with the same gas mixture as that used before intubation, until adequate spontaneous ventilation had returned. The patients then breathed spontaneously for as long as was necessary to achieve a further steady-state (3) of ventilation and circulation.

Estimates of cardiac output, accompanied by sampling of arterial blood (and in some patients mixed venous blood) for estimation of Po_2, Pco_2 and pH, were obtained during the pre-induction control period, after the induction of NLA in the appropriate patients, during the post-induction and pre-intubation steady-state period, and finally during the post-induction steady-state period.

In 4 patients who underwent dental operations, blind nasotracheal intubation was performed after inhalation of approximately 8–10 per cent carbon dioxide in 60 per cent nitrous oxide and 30 per cent oxygen for about 60–90 seconds. The tube entered the larynx on the first attempt in every patient, and a pharyngeal pack was then manually inserted.

RESULTS

The data from this study are presented in two ways. Firstly as a comparison of the circulatory responses to the induction and tracheal intubation sequences in five groups of patients according to the induction agents used, each group comprising both treated and untreated patients. Secondly, as a comparison of the same sequences in two groups: treated (Group 1) and untreated (Group 2) hypertensive patients, irrespective of the agents used for induction.

Induction of anaesthesia.

Thiopentone. In 10 treated hypertensive patients (table II) a mean dose of 155 mg (SD 54) produced a 12 per cent fall of systolic arterial pressure within 3 minutes, and the steady-state values of both systolic and mean arterial pressures for the whole group were more than 25 per cent below the control values, and fell by more than 50 per cent in 2 patients, both female and over 65 years old, though with well controlled arterial pressure in everyday life. A 22 per cent fall in cardiac output was largely responsible for this arterial hypotension, since the systemic vascular resistance fell by only 4 per cent (n.s.). Heart rate increased transiently during the first minute without a significant change of arterial pressure, but the steady-state values of heart rate were not significantly lower than the control values.

In a smaller group of 5 untreated hypertensive patients (table II) arterial pressures fell progressively to a maximum of 35 per cent below the awake controls ($P<0.02$) during the steady-state period of maintenance, but unlike the treated hypertensive group, this arterial hypotension was predominantly due to a significant reduction of systemic vascular resistance (22 per cent, $P<0.05$), and although cardiac output fell by 0.72 l./min (mean), this difference did not reach statistical significance.

Neuroleptanalgesia. Before applying the face-mask, a state of neuroleptanalgesia (NLA) was achieved in which the patients would lie motionless, apparently asleep, but responding to command. In this state the mean arterial pressure was 15 per cent below the control value ($P<0.02$) in a combined group of treated and untreated hypertensive patients (table III). This fall was almost entirely due to a reduction of systemic vascular resistance ($P<0.05$). No significant changes occurred during the first 3 minutes after starting maintenance anaesthesia, but by the time a steady-state had been achieved, a further fall in both systolic and mean arterial pressures had occurred as a result of a 14 per cent reduction of cardiac output ($P<0.001$). No significant changes in heart rate occurred at any stage.

With one exception, there was no obvious difference between the responses of the treated and untreated patients in this group. One patient, a 70-year-old fit lady with untreated essential hypertension, developed a severe sinus bradycardia leading to heart block and hypotension within 4 minutes of the slow intravenous administration of droperidol 5 mg (fig. 1). She responded well to intravenous atropine (0.6 mg), but despite an increase in heart rate from 25 to 89 beats/min, she remained hypotensive (112/70 compared with 204/102 mm Hg) when full NLA had been established, and her cardiac output had fallen from 4.05 l./min to 2.74 l./min. Although the changes were transient in this patient, the findings emphasize the need for continuous monitoring of e.c.g., heart rate and arterial pressure in elderly hypertensive patients.

Propanidid. In a group of 3 untreated hypertensive and 1 treated hypertensive patients, all of whom had high arterial pressures at rest (table III), there was a significant reduction (32 per cent, $P<0.05$) of systolic and mean arterial pressures, together with a marked tachycardia, within 1 minute of completing the rapid intravenous administration of propanidid. After 3 minutes, there was little further change in the arterial pressure, though heart rate had returned to control levels. When a steady-state had been achieved, both systolic and mean arterial pressures were more than 32 per cent below the conscious resting values, with a moderate reduction of heart rate (18 per cent).

Diazepam. In 2 patients, diazepam caused marked but transient hypotension during the induction period (table III), and was associated with excessive hypertension following laryngoscopy.

Methohexitone. In 6 patients induced with methohexitone (2 treated and 4 untreated) there was a significant reduction of systolic (−19 per cent) and mean (−15 per cent) arterial pressure (table III), together with an 18 per cent increase of heart rate. Cardiac output changes were measured in only 1 patient in this group, whose values fell from 5.59 l./min in the awake control period to 3.98 l./min in the steady-state of maintenance anaesthesia. In this patient, there was a slight increase in systemic vascular resistance, thus the hypotension was entirely due to a decrease in cardiac output related to decreased stroke volume. The arterial hypotension was progressive during the first 5 minutes after induction, the values of systolic and mean arterial pressure in the steady-state period being 41 and 36 per cent respectively below the awake control values.

Since systolic pressures fell much more than the diastolic pressures during the first minute, it is probable that the hypotension at this stage was also largely due to reduced cardiac output rather than decreased vascular resistance.

Comparison of treated and untreated patients. There were significant differences ($P<0.05$) between the values of systolic, diastolic and mean arterial pressures in untreated and treated hypertensive patients during the awake control period, but not during any other stage of the investigations. The mean values for all variables after the induction of anaesthesia were remarkably similar in the two groups of patients at each stage of measurement (table IV). In the untreated hypertensive group, the greater fall in arterial pressure from the awake control to the steady-state value was associated with a greater reduction of systemic vascular resistance (2269 to 1993 dyne sec cm^{-5}) compared with the treated hypertensive patients (1925 to 1811 dyne sec cm^{-5}), though the difference between the two groups did not reach statistical significance at the 5 per cent level.

Sequence of tracheal intubation.

Thiopentone. In 10 treated hypertensive patients, no significant change of arterial pressure or heart rate occurred following the administration of suxamethonium (75–100 mg) intravenously. The maximum values of systolic, diastolic and mean arterial pressures, and of heart rate occurring within 30–60 seconds of laryngoscopy and intubation, were significantly higher than the steady-state values during maintenance anaesthesia (table II), and the mean values for the group following laryngoscopy were almost identical with the awake control values for arterial pressure, but heart rate was significantly higher ($P<0.05$) than in the conscious patient. Three patients had systolic arterial pressures not more than 50 mm Hg higher than their conscious values, and one patient exceeded his conscious systolic arterial pressure by 92 mm Hg. The steady-state values achieved after intubation did not differ significantly from those before intubation.

TABLE III

Circulatory responses of four mixed groups (treated and untreated) of hypertensive patients to induction of anaesthesia with neuroleptanalgesia (group A), propanidid (group B), methohexitone (group C) and diazepam (group D), and the subsequent sequence of muscular paralysis, laryngoscopy and endotracheal intubation, and maintenance anaesthesia. Mean values are shown with SD in brackets.

	NEUROLEPTANALGESIA *n*=9 (5 T, 4 UT)						PROPANIDID *n*=4 (1 T, 3 UT)						METHOHEXITONE *n*=6 (2 T, 4 UT)						DIAZEPAM *n*=2 (2 UT)			
	SAP	DAP	MAP	HR	$\dot{Q}$	SVR	SAP	DAP	MAP	HR	$\dot{Q}$	SVR	SAP	DAP	MAP	HR	$\dot{Q}$	SVR	SAP	DAP	MAP	HR
Awake (control)	191 (27)	99 (9)	133 (12)	72 (12)	5.27 (1.13)	2010 (442)	235 (60)	117 (24)	159 (39)	71 (20)	4.38[1]	2901[1]	192 (13)	99 (18)	130 (14)	84 (21)	5.59[1]	1715[1]	190	105	133	84
Awake (after NLA)	164* (33)	88* (13)	113* (18)	74 (16)	5.03 (1.34)	1795* (308)																
After induction 1 min	—	—	—	—	—	—	161* (26)	95* (17)	117* (23)	113* (17)	—	—	155** (20)	89 (15)	111* (14)	99 (15)	—	—	145	75	98	81
3 min	167* (23)	93 (11)	116** (15)	74 (12)	—	—	166* (41)	94 (19)	117 (27)	73 (15)	—	—	132*** (14)	78** (14)	96*** (12)	91 (11)	—	—	—	—	—	—
Steady-state (1)	151*** (29)	84*** (14)	108*** (18)	73 (16)	4.53*** (0.96)	1905 (302)	150* (32)	83* (14)	105* (20)	58 (13)	—	—	114*** (24)	67** (15)	83** (17)	78 (21)	3.98[1]	1807[1]	135	70	92	82
Steady-state (2)	149 (35)	83 (15)	107 (20)	71 (14)	4.30 (1.01)	1989 (330)	150 (32)	83 (14)	105 (20)	58 (13)	—	—	112 (26)	64 (15)	80 (17)	78 (24)	3.98[1]	1807[1]	135	70	92	82
After suxamethonium	141 (38)	75 (14)	97 (21)	72 (14)	—	—	165 (56)	96 (38)	118 (45)	67 (16)	—	—	115 (31)	67 (20)	83 (23)	76 (17)	—	—	—	—	—	—
After laryngoscopy (maximum values)	194†† (35)	103†† (14)	135†† (22)	90† (25)	—	—	229††† (44)	134† (35)	166†† (37)	89†† (7)	—	—	171† (66)	98† (32)	122† (42)	96† (9)	—	—	250	130	170	115
Steady-state (3)	141 (46)	79 (20)	102 (26)	77 (17)	4.53 (1.17)	1799 (280)	148 (36)	82 (20)	106 (23)	62 (17)	2.57[1]	3296[1]	110 (40)	65 (23)	80 (28)	65 (16)	3.56)[1]	1796[1]	173	90	117	87

Key Symbols, abbreviations and units as in table II. [1]=measurements in one patient only. T=treated. UT=untreated.

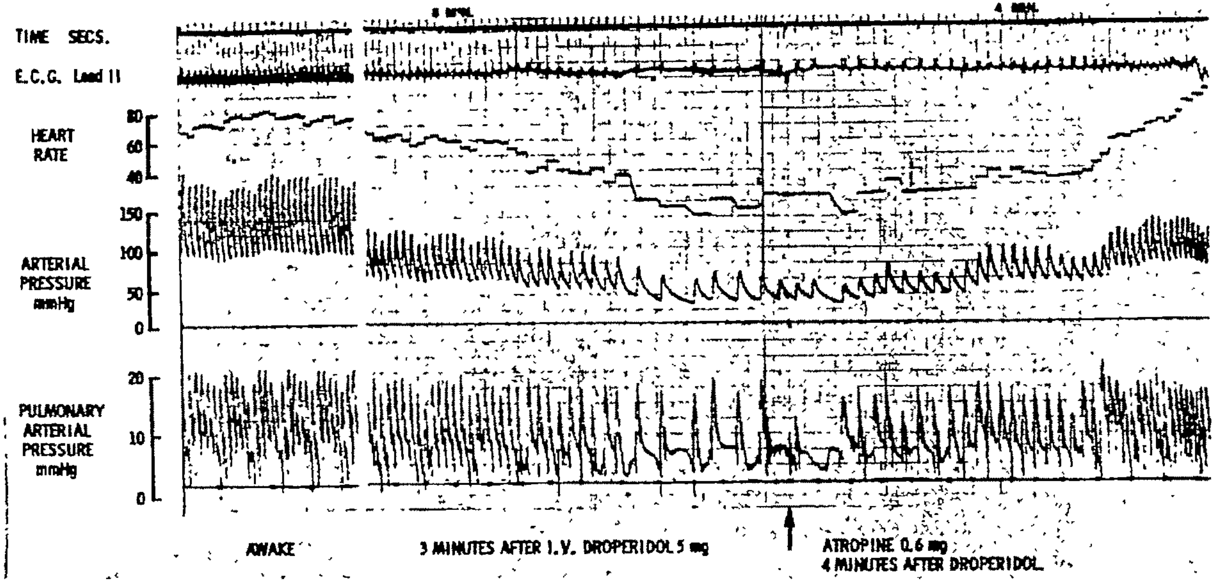

FIG. 1

Development of marked sinus bradycardia leading to heart block following the administration of droperidol (5 mg) in patient No. 21, and the return to sinus rhythm following atropine (0.6 mg).

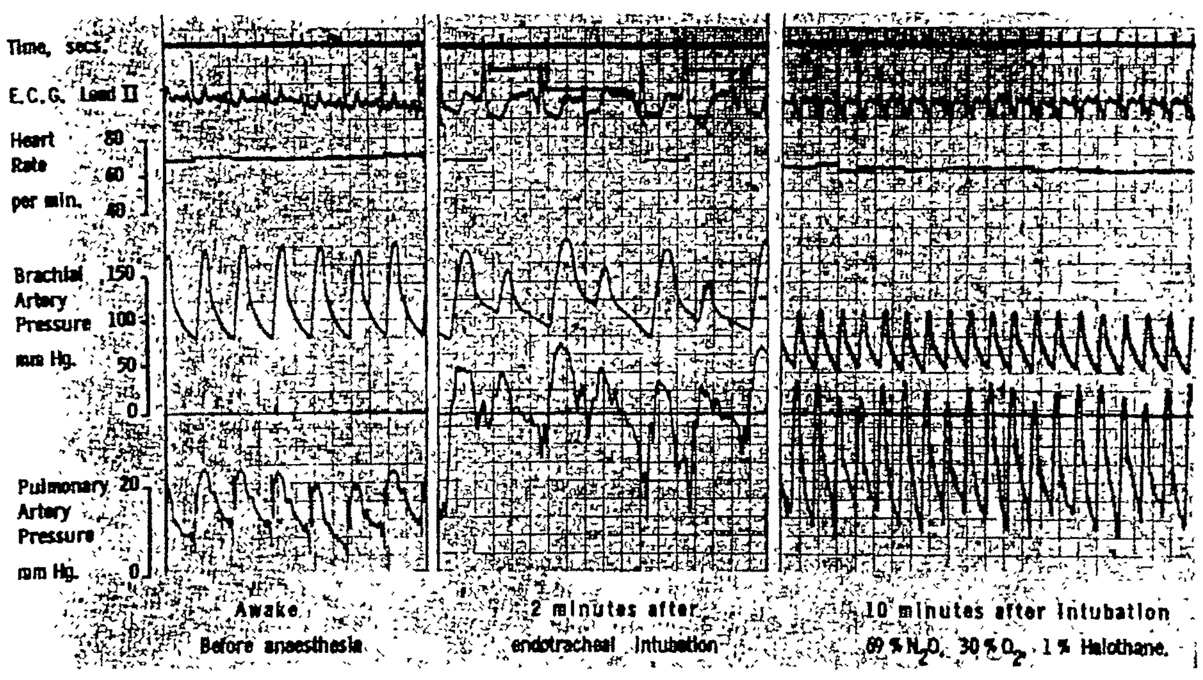

FIG. 2

Circulatory changes occurring during and after laryngoscopy and tracheal intubation (patient No. 15). The lefthand panel shows the values during the awake control period, at which time the patient's cardiac output was 4.27 l./min. Arterial hypertension occurred within 15 seconds of laryngoscopy, despite having fallen to 100/50 mm Hg after induction. Tracheal intubation was accompanied by prolonged ventricular bigeminy and further systemic hypertension. Pulmonary hypertension was also noted at this stage (centre panel) and persisted into the steady-state of maintenance anaesthesia. Depression of the S-T segment and T-wave inversion also persisted into maintenance anaesthesia, indicating myocardial ischaemia in association with the low arterial pressures. Cardiac output fell to 2.84 l./min during maintenance anaesthesia; thus, in association with the elevated pulmonary arterial pressures, it may be estimated (even in the absence of left atrial pressures) that the resistance of the pulmonary vascular bed had more than doubled.

Similar directional changes were observed in 4 untreated hypertensive patients (table II), and although the data are not amenable to statistical comparison because of the small numbers in this group, the mean values for all variables are sufficiently similar to those of the treated hypertensive group, at each stage, that it is unlikely that a real difference exists.

Neuroleptanalgesia. No significant changes in arterial pressure or heart rate accompanied the administration of suxamethonium to 9 patients induced by neuroleptanalgesia (table III). The changes which followed laryngoscopy and intubation were of a similar magnitude to those in patients receiving thiopentone, and there was no significant difference between these values for arterial pressure and those in the awake control period, although heart rate was elevated by 18 beats/min ($P<0.02$). In individual patients, the systolic arterial pressure after intubation exceeded their awake controls in 5 patients, 1 of whom had an increase of 66 mm Hg.

Propanidid. No significant haemodynamic changes accompanied the administration of suxamethonium in 4 patients induced with propanidid. Arterial pressures increased significantly (table III) following laryngoscopy and intubation, and the mean values for the group were not significantly different from the awake control values. Systolic arterial pressure exceeded the awake control in 2 patients, one by 22 mm Hg, and in the other by 76 mm Hg reaching a maximum value of 276/176 mm Hg. Heart rate also increased significantly in the group as a whole, although the fastest rate recorded (96) was rather lower than the fastest rates recorded in the thiopentone group (7 out of 10 developed heart rates in excess of 100) and the NLA group (maximum rate 140 beats/min, 3 out of 9 over 100 beats/min).

Methohexitone. There was a greater percentage increase in systolic and mean arterial pressures (53 per cent, $P<0.05$) following laryngoscopy and intubation (table III), as compared with the other groups (thiopentone 39.4 per cent; NLA 27 per cent; propanidid 51 per cent). Individual systolic pressures exceeded the awake control values in 2 patients, +39 mm Hg in one and +72 mm Hg in the other.

Comparison of treated and untreated patients. Mean values for arterial pressures, heart rate and cardiac output in the pre-intubation steady-state were not significantly different in the two groups of patients (table IV), and the administration of suxamethonium had no significant effect in either group. Following laryngoscopy and intubation, arterial systolic, diastolic and mean pressures, and heart rate were significantly elevated as compared with the pre-intubation steady-state, and there was no difference between the responses of the treated and untreated patients. Postintubation steady-state values were similar in both groups, and were not significantly different from the pre-intubation levels. Following intubation, there was a higher incidence of hypertension exceeding the awake control value in the treated hypertensive patients. Mean arterial pressure was elevated above control values in 70 per cent of this group as compared with 42 per cent of the untreated hypertensive patients, and 4 treated hypertensives had excessive hypertension following laryngoscopy and intubation (>50 mm Hg above awake control systolic arterial pressure) compared with only 1 untreated hypertensive patient. Three of these four treated patients were well controlled and almost normotensive as a result of treatment, and there were no obvious explanations as to why they should produce such a marked sympathetic response to intubation.

Disorders of cardiac rhythm.

Many of the patients in both treated and untreated groups had disorders of cardiac rhythm during the awake control period, usually premature ventricular contractions. The incidence was higher in the untreated group (6 out of 13) than in the treated group (2 out of 16) ($\chi^2=2.56$, n.s.), although there was no consistent relationship between the incidence of cardiac dysrhythmia in the conscious patient, and the arterial pressure. Four patients developed premature ventricular contractions during the induction of anaesthesia having previously been free from dysrhythmia, and in 4 others the incidence of dysrhythmia increased during induction.

Administration of suxamethonium was not associated with the onset of dysrhythmia in any patient, but was associated with the cessation of pre-existing dysrhythmia in 8 patients (6 untreated and 2 treated).

Laryngoscopy, laryngeal and tracheal spraying,

TABLE IV

Responses of treated and untreated hypertensive patients to induction of anaesthesia, and the sequence of muscular paralysis, laryngoscopy, endotracheal intubation and subsequent maintenance anaesthesia. Mean values are shown with SD in parentheses.

	TREATED HYPERTENSIVES (n=16)						UNTREATED HYPERTENSIVES (n=14)					
	SAP	DAP	MAP	HR	$\dot{Q}$	SVR	SAP	DAP	MAP	HR	$\dot{Q}$	SVR
Awake (control)	181 (31)	93 (14)	125 (18)	72 (16)	5.19 (1.18)	1925 (207)	211 (36)	104 (18)	142 (24)	74 (14)	5.00 (0.87)	2269 (114)
After induction												
1 min	169 (36)	92 (24)	118 (27)	82* (18)	—	—	165*** (26)	92* (15)	117*** (19)	92* (18)	—	—
3 min	161** (35)	90 (22)	113** (25)	78 (17)	—	—	159*** (30)	86*** (13)	110*** (18)	77 (10)	—	—
Steady-state (1)	139*** (35)	76*** (18)	97*** (22)	67 (14)	4.28** (1.02)	1811 (105)	137*** (28)	76*** (14)	97*** (18)	69 (15)	3.89** (0.70)	1993 (200)
Steady-state (2)	134 (33)	74 (17)	95 (21)	67 (14)	4.14 (1.11)	1833 (115)	137 (36)	75 (17)	97 (22)	68 (16)	3.80 (0.82)	2040 (185)
After suxamethonium	132 (41)	76 (24)	95 (29)	72 (12)	—	—	136 (31)	74 (16)	94 (20)	69 (15)	— —	— —
After laryngoscopy (maximum values)	186††† (39)	105††† (23)	133††† (28)	91††† (16)	—	—	194††† (43)	106††† (24)	136††† (29)	90††† (19)	—	—
Steady-state (3)	133 (36)	74 (19)	95 (24)	69 (14)	4.03 (1.22)	1883 (128)	126 (34)	70 (20)	90 (23)	66 (18)	3.80 (0.95)	1892 (170)

	Treated	Untreated
Thiopentone	10	4
Neuroleptanalgesia	5	4
Propanidid	1	3
Methohexitone	0	3

Significance levels are denoted by the following symbols:

Paired two-tailed t-test:	comparison of values against awake control	$P<0.05$	*
		$P<0.01$	**
		$P<0.001$	***
	comparison of values with steady-state (2)	$P<0.05$	†
		$P<0.01$	††
		$P<0.001$	†††

Key Symbols, abbreviations and units as in table II.

and tracheal intubation were associated with a high incidence of dysrhythmia, usually premature ventricular contractions or ventricular bigeminy (fig. 2). These dysrhythmias occurred in 6 out of 13 untreated patients, and 5 out of 16 treated patients, and in every case they followed the onset of tachycardia and hypertension. In only 1 patient of the 44 hypertensive patients studied to date have we observed a bradycardia in response to laryngoscopy and intubation (fig. 3). One patient, a 65-year-old untreated hypertensive lady (195/80 mm Hg awake), developed wandering pacemaker shortly after induction with methohexitone 100 mg, together with occasional premature ventricular contractions, but immediately after laryngoscopy she developed ventricular tachycardia for a period of 10 seconds followed by further premature ventricular contractions.

Quantification of the changing incidence of dysrhythmia in patients with pre-existing dysrhythmia presents more difficulty than the quantification and statistical analysis of those arising de novo. We have applied cumulative sum (cusums) procedures (Woodward and Goldsmith, 1964) to identify statistically significant changes in the incidence of dysrhythmias associated with clinical events (fig. 4). Since these procedures are not widely known and used in the medical field, details of their application, and the manner in which the results are presented, the "Manhattan diagram", are described in brief in an appendix to this paper.

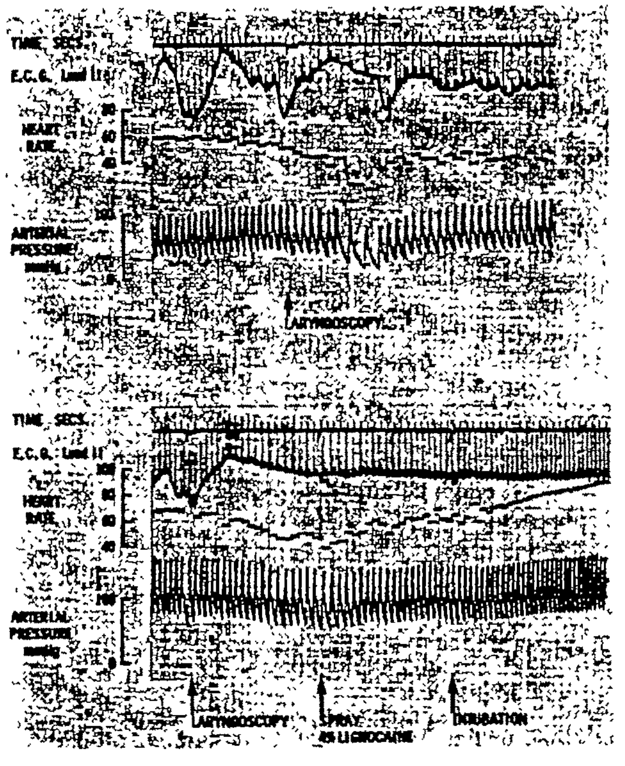

FIG. 3

Vagal reflex response to laryngoscopy. The upper panel shows the development of marked bradycardia shortly after introduction of the laryngoscope in patient No. 27 who had not previously received atropine. Following atropine 0.6 mg (lower panel), the initial heart rate was higher, but laryngoscopy still produced a bradycardia of slightly less severity before the sympathetic responses appeared.

Effect of blind nasotracheal intubation.

In 4 patients, nasotracheal intubation after inhalation of 10 per cent carbon dixoide caused no significant increase in systolic or mean arterial pressure, nor of heart rate. In 2 of these patients, previous laryngoscopy had produced a marked hypertensive response.

DISCUSSION

Our previous communication (Prys-Roberts, Meloche and Foëx, 1971) concluded that untreated high arterial pressures constituted a serious risk to patients undergoing anaesthesia and surgery. This conclusion was based on our finding of a high incidence of evidence of myocardial ischaemia related to arterial hypotension during steady-state anaesthesia in both treated and untreated patients. The results of the present study serve to emphasize that hypertensive patients are as much if not more at risk during induction of anaesthesia, and during subsequent laryngoscopy and tracheal intubation, as they are during steady-state anaesthesia. It is difficult to compare the relative risk of hypotension with myocardial ischaemia during established anaesthesia, with the excessive swing from hypertension in the conscious state to sudden hypotension during induction, followed by excessive hypertension during and after laryngeal stimulation. It is clear that these responses are not consequent upon the drugs used to manage patients with high blood pressure, but are to some extent related to the initial blood pressure. Following our findings during steady-state anaesthesia, it was surprising to find that patients on anti-hypertensive therapy with well controlled blood pressures, were equally prone to develop a hypertensive response to

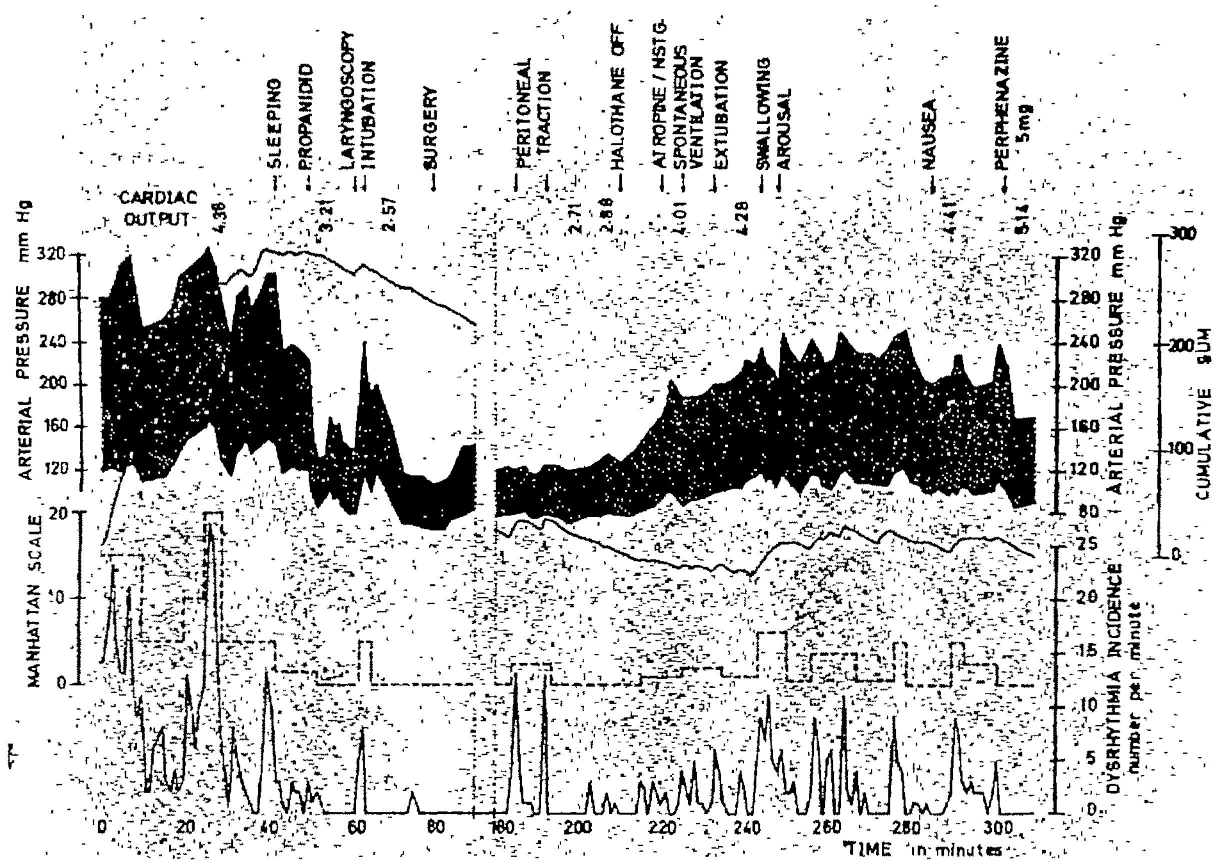

FIG. 4

Interrelation of arterial pressure and the incidence of cardiac dysrhythmia in patient No. 35. The lowest graph (continuous line) indicates the incidence of dysrhythmia, interpreted as the number of abnormal e.c.g. complexes per minute. The upper continuous line represents the cumulative sum (cusum) of this dysrhythmia incidence, and the intermediate dotted-line graph is the Manhattan diagram representing the changes in slope of the cusum graph, assessed at an arbitrary 5 per cent significance level. Assessment at the more critical 1 and 0.1 per cent significance levels showed changes to occur at the same points, but the "corners" of the Manhattan graph, representing the time of onset of a significant change in the cusum, were less obvious and of smaller magnitude.

During the pre-anaesthetic control period, the highest incidence of dysrhythmia was related to the highest arterial pressure levels which varied in a random manner, and were not associated with recognizable events. At the first event marked "sleeping", the patient fell into a natural sleep at the end of the control measurements of pulmonary gas exchange, and a significant reduction occurred in both the arterial pressure and the incidence of dysrhythmia. Although the patient could not be aroused by normal spoken command at this stage, anaesthesia was induced with propanidid in the usual way, and this event was associated with a further significant reduction of both arterial pressure and the incidence of dysrhythmia. Laryngoscopy and intubation caused a significant increase in both variables. During surgery, a 90-minute period of the record is not shown since no dysrhythmia occurred, which accounts for the progressive decline of the cusum value between the start and finish of the period. At the end of surgery, traction on the peritoneum of the pelvic floor, and of the peritoneal edges of the abdominal wall during closure, caused reflex increases in arterial pressure associated with the reappearance of dysrhythmia. Extubation, tracheal suction, and the period of arousal were associated with a progressive increase in arterial pressure and the incidence of dysrhythmia, with coincident peaks in both variables.

Cardiac output values are in l./min.

intubation, even though they were less likely to suffer drastic reduction of arterial pressure during induction.

Circulatory responses to laryngoscopy and tracheal intubation.

Reflex cardiovascular responses to mechanical stimulation of the upper respiratory tract have been described in cats (Tomori and Widdicombe 1969) and to the aspiration of secretions from the trachea in patients with normal cardiovascular reflexes (Corbett, Kerr and Prys-Roberts, 1969) and in patients with exaggerated cardiovascular reflexes due to autonomic overactivity (Corbett et al., 1969). The predominant response in man is a tachycardia and arterial hypertension, the latter being due to increased cardiac output rather than increased systemic vascular resistance, and is associated with a transient rise in the central venous pressure (Corbett et al., 1969). That these reflex responses are mediated by increased sympathetic nervous activity is based on circumstantial evidence in man, but is supported by the findings of Tomori and Widdicombe (1969) in the cat. They observed that mechanical stimulation of four areas of the upper respiratory tract, the nose, the epipharynx, the laryngopharynx and the tracheobronchial tree, induced reflex cardiovascular responses associated with enhanced neuronal activity in the cervical sympathetic efferent fibres. These cardiovascular responses, tachycardia and hypertension, and the enhanced neuronal activity were most pronounced during stimulation of the epipharynx, whereas those arising from stimulation of the tracheobronchial tree were least marked. In the present study, attempts were made to differentiate between the effects of laryngoscopy and those of tracheal intubation, and it was clear that the majority of the patients studied by us produced a reflex tachycardia and hypertension well before the act of intubation, though the effect was often enhanced by either spraying the larynx, or by intubation. Once the endotracheal tube was in position, and the laryngoscope withdrawn, the hypertension and tachycardia quickly subsided, but disturbing dysrhythmia tended to persist for up to 2 or 3 minutes. In the hypertensive patient, the extent of these cardiovascular reflexes is much more marked than in the normotensive patient.

Of the studies in normotensive man during anaesthesia, those of King and his colleagues (1951), Colon-Yordan, Mackrell and Stone (1953) and Wycoff (1960) were based on continuous records of intra-arterial pressure. Their findings were similar to ours, although the magnitude of the changes was much smaller. The study of King and associates included some patients who were hypertensive before intubation during maintenance anaesthesia with cyclopropane or diethyl ether, but they gave no indication as to whether these patients were known to be hypertensive before anaesthesia. During deep anaesthesia with cyclopropane or diethyl-ether, King and his colleagues found that the cardiovascular responses of these patients to laryngoscopy and intubation were effectively suppressed, while Colon-Yordan, Mackrell and Stone found a significant incidence (33 per cent) of ventricular dysrhythmia during intubation under deep cyclopropane-ether anaesthesia. Wycoff (1960) compared laryngoscopy and tracheal intubation under general anaesthesia with the same procedure under surface analgesia produced by cricothyroid block, and although the latter technique produced smaller changes in both blood pressure and heart rate, a sympathetic response was still present. Wycoff attributed this to soft tissue pressure by the laryngoscope (Macintosh), and also concluded that premedication with a belladonna derivative did not alter its incidence.

Takeshima, Noda and Higaki (1964) compared the effects of laryngoscopy with different laryngoscope blades, and concluded that the Macintosh blade which compressed the soft tissues of the anterior epipharynx produced a significantly greater hypertensive response than the straight-bladed Wis-Foregger laryngoscope. Simpler studies of young normotensive subjects (Takeshima, Noda and Higaki, 1964; Forbes and Dally, 1970) have established that the mean increase in arterial pressure due to laryngoscopy and intubation was of the order of 20–25 mm Hg, with maximum changes of about 40–45 mm Hg in a few subjects. In a group of normotensive patients with mitral stenosis or constrictive pericarditis, Dottori, Löf and Ygge (1970) observed significant hypertension in response to laryngoscopy and intubation following induction with nitrous oxide/oxygen/muscle relaxant (m.a.p. increased 40 per cent above conscious level), thiopentone/nitrous oxide/oxygen/relaxant (m.a.p. increased 57 per cent), and hexobarbitone/nitrous oxide/oxygen/relaxant (m.a.p. increased 18 per cent). Sinus tachycardia occurred in all patients, but was most marked in patients receiving thiopentone, and least marked following induction with nitrous oxide alone.

Hypertensive patients, whether treated or not, are prone to much greater changes in arterial pressure than normotensive patients of the same age. Dingle (1966) in a series of 19 hypertensive patients, found a mean increase in systolic arterial pressure of 35 mm Hg, with excessive increases in a few patients, but gave no details of the resting values, nor of the induction and maintenance techniques he used. The excessive swings of arterial pressure in some of our patients gave rise to considerable concern, particularly since they were accompanied by electrocardiographic evidence of prolonged ischaemia (fig. 2). Neuroleptanalgesia was used in the second group of patients in the hope that under its influence the hypertensive response to laryngoscopy would be attenuated, and that less circulatory depression would occur during maintenance anaesthesia. The lack of stability during laryngoscopy with this method was surprising in view of the cardiovascular stability which is commonly associated with NLA during surgery. However, the percentage increase in arterial pressure following NLA induction was less than with the other agents, and the different character of the arterial hypotension implies a lesser degree of myocardial depression and a decreased resistance to left ventricular ejection. These characteristics commend the technique for the induction of anaesthesia in hypertensive patients, but further measures to prevent the occurrence of severe hypertensive crises during intubation would seem to be necessary. Although the use of deep anaesthesia may suffice in the normotensive patient, our previous findings would strongly suggest that the associated hypotension and myocardial ischaemia would be undesirable in the hypertensive patient. It must be remembered, too, that in all our patients the hypertensive response to laryngoscopy and intubation occurred despite the prior establishment of a steady-state of maintenance anaesthesia with 1 per cent halothane.

Since the hypertensive response is due to increased activity in the cardiac sympathetic nerves (Tomori and Widdicombe, 1969) in the cat, and the pattern of their cardiovascular findings was almost identical with ours, it seems rational to block these responses by using a specific beta-adrenergic blocking agent. Propranolol has proved extremely effective in suppressing the hypotension, tachycardia and dysrhythmias associated with patients with sympathetic over-activity in severe tetanus (Prys-Roberts et al., 1969). In these patients, the exaggerated circulatory response to tracheal and nasopharyngeal suction of secretions was effectively suppressed by small doses of propranolol. The main disadvantage attending the intravenous use of propranolol is its quinidine-like effect of myocardial depression (Fitzgerald, 1970), although this has not been a problem in the management of patients with severe tetanus when smaller doses (0.1–0.2 mg) have been given incrementally. Propranolol and other beta-adrenergic blockers have been widely used and advocated for the management of hypertension (Gillam and Prichard, 1964; Richards, 1966; Frohlich, Tarazi and Dustan, 1969; Leishman et al., 1970), and of angina pectoris in hypertensive and normotensive subjects (Gillam and Prichard, 1965; Rabkin et al., 1966; Björntorp, 1967).

Choice of induction agent.

None of the agents used for induction of anaesthesia in this series was entirely satisfactory, although the NLA combination was less unsatisfactory than the others. Caution is required during the induction of NLA in hypertensive patients, however, and our experience with patient 21 (fig. 1) emphasizes the vascular instability of these patients, and the need for careful drug administration and continuous monitoring. We cannot agree with the recommendation of Lawin and associates (1966) that patients should be taken off antihypertensive and vasodilator drugs at least 4 days before induction of NLA. They reported three cases of cardiac arrest during induction of NLA in patients receiving vasodilator therapy. Cardiac arrest occurred within one circulation time of the rapid injection of large doses (10–22 mg) of droperidol, and although cardiac arrest was attributed to failure of cardiac filling as a result of excessive arteriolar dilatation, it is more likely to have been the result of a bolus of drug entering the coronary circulation. In our patient the onset of heart block following severe sinus bradycardia occurred 3 minutes after the end of the injection, in a patient who immediately previously had an appearance time of less than 10 seconds for a dye-dilution curve.

Propanidid was particularly vicious in its hypotensive effect which was maximal during the first minute after its administration, and before maintenance anaesthesia had been commenced. Although the steady-state arterial pressures were no lower than those following other induction agents, in view of the sudden hypotension and the marked tachycardia we cannot recommend its use in the hypertensive patient.

Contrary to the established finding that methohexitone causes less arterial hypotension in normotensive subjects than thiopentone, when used in doses comparable to this present study (Dundee and Moore, 1961), we have found that methohexitone produced a significantly greater fall in systolic and mean arterial pressure in hypertensive patients, associated with a transiently higher heart rate during the first 1–3 minutes. Although we measured cardiac output in only one of the patients receiving methohexitone (in whom no change of systemic vascular resistance occurred), our findings were otherwise similar to those of Rowlands and associates (1967) in a series of patients with pre-existing cardiac disease, all of whom had supraventricular dysrhythmias beforehand. They concluded that the moderate hypotension which occurred in their patients was almost entirely the result of a fall in cardiac output and stroke volume. It has been widely established that thiopentone causes arterial hypotension as a result of reduced cardiac output (Fieldman, Ridley and Wood, 1955; Prys-Roberts, Kelman and Greenbaum, 1967), although in normotensive subjects the rate of injection may be a significant factor (Etsten and Li, 1955). We have also measured arterial pressures by sphygmomanometry in two hypertensive patients who were induced with 10 mg and 20 mg respectively of diazepam, and in view of the marked but transient hypotension (−40 mm Hg mean arterial pressure) and the excessive hypertension following laryngoscopy in both cases (+37 and +50 per cent of the awake control values of systolic arterial pressure) we did not proceed to more complete studies. We are unable to comment as yet on the possibilities of inhalational induction for hypertensive patients, though the use of cyclopropane or halothane/nitrous oxide must be considered.

APPENDIX

Cumulative Sum procedures (Cusums)

Cumulative sum procedures (Woodward and Goldsmith, 1964) may be used to detect alterations in mean levels between groups of values in a time series, and to identify the time of onset of such alterations. The procedures are performed by a digital computer which is programmed to read in a time series, and to calculate cumulative sums of the series using the grand mean of the series as a reference value. The computer also determines the occurrence of changes in the slope of the cusum/time relation, the assessment of which is based on Student's *t*-tests, nominally applied at the 0.1, 1 and 5 per cent significance levels.

This procedure is carried out by scanning the time series in a "forward" direction in such a way as to compare each cusum value with previous significant changes in the series, and to perform *t*-tests between groups of intervening cusum values. When the *t*-test values are not significant, the computer moves to the next cusum and repeats the process. When a significant change is detected, the computer is programmed to check that the change in slope is maintained beyond the test point, and that the onset of the change (the "corner") is identified on the time scale. This scanning procedure is repeated in the reverse direction, since certain real step changes may only appear to be significant in one direction. The results of both forward and reverse scanning are then amalgamated, and the computer is programmed to print out the results in graphical form (viz. fig. 4). The Manhattan diagram, although resembling a histogram in appearance, actually represents the "corners", or points where the slope of the cusum/time relation changes significantly.

Previous applications of this method of statistical analysis in the medical field have analyzed trend changes in the mean arterial pressure in patients in whom the systolic and diastolic pressures have been varying in a random fashion around a mean level (Corbett, 1968): for example, the labile hypertension of patients with severe tetanus.

The present application enabled us to determine whether changes in the incidence of dysrhythmia as a result of induction, laryngoscopy or intubation were statistically significant events, or whether they represented random changes in the background dysrhythmia level which were due to chance.

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ETUDES DE L'ANESTHESIE PAR RAPPORT A L'HYPERTENSION

II: CONSEQUENCES HEMODYNAMIQUES DE L'INDUCTION ET DE L'INTUBATION ENDOTRACHEALE

SOMMAIRE

Les réactions électrocardiographiques et hémodynamiques à l'induction d'anesthésie, suivie de laryngoscopie et intubation endotrachéale ont été étudiées chez un groupe de seize patients hypertendus non-traités, ainsi que chez un groupe de vingt patients sous traitement antihypertenseur jusqu'au jour de l'opération inclus. Les effets de cinq agents d'induction différents, thiopentone, methohexitone, propanidid, diazepam et la neuroleptanalgésie par une association de phenoperidol et droperidol ont été comparés. La neuroleptanalgésie causa moins d'hypotension artérielle que les autres agents, mais ne procura qu'une protection marginalement meilleure contre l'hypertension, la tachycardie et la dysrhythmie, associés à la laryngoscopie et l'intubation trachéale. Propanidid et diazepam causèrent une hypotension dramatique mais passagère chez un petit nombre de patients et leur étude ne fut plus poursuivie. Methohexitone, contrairement à ses effets chez des sujets normotendus, causa chez les patients hypertendus une plus forte hypotension que thiopentone. Les auteurs donnent la rationale du bloquage prophylactique des récepteurs beta-adrénergiques pour prévenir les crises hypertensives au cours de la laryngoscopie et l'intubation, aussi bien chez les hypertendus traités que non-traités.

UNTERSUCHUNGEN ZUR FRAGE ANAESTHESIE UND HYPERTENSION

II: HÄMODYNAMISCHE FOLGEERSCHEINUNGEN VON NARKOSE-EINLEITUNG UND ENDOTRACHEALER INTUBATION

ZUSAMMENFASSUNG

Elektrokardiographische und hämodynamische Reaktionen unter der Narkoseeinleitung mit anschließender Laryngoskopie und endotrachealer Intubation wurden bei einer Gruppe von 16 unbehandelten Patienten mit erhöhtem Blutdruck und einer Gruppe von 20 Patienten unter einer antihypertensiven Therapie vor der Operation bis einschließlich dem Operationstag untersucht. Der Einfluß von 5 verschiedenen Medikamenten für die Narkoseeinleitung—Thiopenton, Methohexitan, Propanidid, Diazepam, sowie von Neuroleptanalgesie durch Kombination von Phenoperidin und Droperidol — wurde verglichen. Die Neuroleptanalgesie verursachte eine geringen arterielle Hypotesion als alle anderen Mittel, bot jedoch nur einen wenig besseren Schutz gegen Hypertension, Tachykardie und Dysrhythmie bei der Laryngoskopie und Trachealintubation als die anderen Mittel. Sowohl Propanidid als Diazepam verursachten eine dramatische, jedoch transitorische Hypotension bei einer kleinen Zahl von Patienten und wurden nicht weiter untersucht. Im Gegensatz zu ihren Wirkungen auf Personen mit normalen Blutdruck war die Blutdrucksenkung bei hypertensiven Patienten bei Methohexitan stärker als bei Thiopenton. Die theoretische Grundlage für eine prophylaktische Blockade der Beta-adrenergischen Rezeptoren zur Vermeidung von hypertensiven Krisen während der Laryngoskopie und Intubation bei behandelten und unbehandelten Hochdruckpatienten wird dargelegt.

ESTUDIOS SOBRE LA ANESTESIA EN RELACION CON LA HIPERTENSION

II: CONSECUENCIAS HEMODINAMICAS DE LA INDUCCION E INTUBACION ENDOTRAQUEAL

RESUMEN

Las respuestas electrocardiográficas y hemodinámicas a la inducción de la anestesia seguida por laringoscopia e intubación endotraqueal han sido estudiadas en un grupo de dieciséis pacientes hipertensos sin tratamiento y en un grupo de veinte pacientes bajo terapia antihipertensora hasta e incluyendo el día de la operación. Fue comparada la influencia de cinco agentes de inducción diferentes, tiopentona, metohexitona, propanidid, diacepam, y neuroleptanalgesia inducida por una combinación de fenoperidina y droperidol. La neuroleptanalgesia causó menos hipotensión arterial que cualquiera de los otros agentes, pero dio una protección sólo ligeramente superior a la de los otros agentes contra hipertensión, taquicardia y disritmia asociadas con la laringoscopia e intubación traqueal. El propanidid y diacepam causaron hipotensión dramática pero transitoria en un pequeño número de pacientes y no fueron investigados más. En oposición a sus efectos en sujetos normotensos,, a methohexitona causó mayor hipotensión que la tiopentona en pacientes hipertensos. Se explica el fundamento para un bloqueo profiláctico de los receptores beta-adrenérgicos para impedir crisis hipertensivas durante la laringoscopia e intubación en pacientes hipertensos con y sin tratamiento.

NOTICE

It is proposed to establish a Zambian Society of Anaesthetists with the ultimate object of forming a Regional Society. The inaugural meeting took place on May 29, 1971, in the Medical School of the University of Zambia at Lusaka. Any anaesthetist in Central or East Africa who is interested in supporting this venture should contact Dr F. F. Casale, F.F.A.R.C.S., University Teaching Hospital, Private Bag R. W. 1, Lusaka, Zambia, for further information.

British Journal of Anaesthesia 1998; **80**: 123–128

CORRESPONDENCE

Is sevoflurane replacing halothane?

Sir,—Mostafa and Atherton describe the successful use of sevoflurane as an induction agent in three adult patients with difficult airways.[1] My practice includes anaesthesia for children with difficult airways.

I recorded some details of the first 30 such children in whom anaesthesia was induced with sevoflurane when it became available in late 1995. My method is to use 8% sevoflurane in 100% oxygen or in a 2:1 nitrous oxide–oxygen mixture delivered from a T-piece by a bare hand. Sevoflurane is discontinued when the patient loses consciousness, halothane or isoflurane being introduced.

Anaesthesia was induced in 30 children (15 boys, 15 girls). Mean age was 3.3 yr (range 1 month to 12 yr); 11 children were aged 3 months or less. The diagnoses are listed in table 1.

Table 1 Diagnoses of children with "difficult airways" who received sevoflurane for induction of anaesthesia

Cleft lip and palate	9
Laryngeal papillomata	6
Subglottic stenosis	5
Laryngeal web	2
Micrognathia	2
Tracheocutaneous fistula	2
Beckwith's syndrome	1
Choanal atresia	1
Laryngomalacia	1
Mandibular fracture	1
Total	30

Mean time to loss of consciousness was 34.1 (SD 9.23; range 21–62) s. In all of these inductions, the only untoward event was one child who coughed twice. No patient suffered breath-holding or desaturation.

My previous calculations[2] confirm Mostafa and Atherton's impression that sevoflurane is not especially expensive when used as an *induction agent*. Sevoflurane is now my routine inhalation induction agent for children with difficult or "easy" airways.

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2. Barker I. The cost of volatile anaesthetic agents. *British Journal of Anaesthesia* 1996; 76: 749.

Propofol in paediatric intensive care

Sir,—I was pleased to see another rational study of propofol in a small group of children in intensive care, together with a supportive editorial.[1,2] It always seemed to me that propofol was the scapegoat for the shortcomings of paediatric intensive care practice in the UK in the late 1980s. The problem of relative lipid overloading alluded to in many of the case reports and subsequent articles may be circumvented by use of 2% propofol solution, but this was not mentioned in the current article or accompanying editorial. Surely the ethical window has re-opened to allow a properly controlled multicentre evaluation funded by the manufacturer, akin to the adult study, but preferably using the 2% solution. The FDA has recently changed its policy on paediatric studies of new drugs.[3] It was interesting that the current evaluation received an exemption from the MCA in the UK and this should encourage paediatric intensivists to collaborate to produce an ethically acceptable and scientifically sound study.

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Combined spinal–extradural analgesia in labour and post-dural puncture headache

Sir,—Jenkins,[1] and Elton and May[2] have recently commented on the incidence of post-dural puncture headache (PDPH) associated with combined spinal–extradural analgesia in labour. Jenkins suggested that the use of low-dose extradural only analgesia is preferable to a combined spinal–extradural technique because of the high incidence of PDPH (2.3%) reported by Collis and colleagues.[3] Elton and May, in reply, cited the study by Norris and colleagues[4] to suggest that combined spinal–extradural analgesia in labour may not be associated with an excessive incidence of PDPH.

The combined spinal–extradural technique in obstetrics was used initially by Brownridge[5,6] for anaesthesia for elective Caesarean section. He used a dual space technique. In an uncontrolled series of 200 women undergoing this technique, there were no cases of PDPH. Brownridge attributed this fact to extradural bolus doses of pethidine which these women received for postoperative analgesia. However, this encouraged the notion that combined spinal–extradural techniques might be associated with lower PDPH rates than either technique alone.

The incidence of PDPH cited by Jenkins, namely 2.3% in the study by Collis and colleagues[3] from Queen Charlotte's Hospital, is certainly unacceptable in an obstetric regional analgesia service. However, there were particular reasons why the PDPH rate was so high in that particular study. The study was a prospective observational study of combined spinal–extradural analgesia in labour in 300 women. A single space needle-through-needle technique using 16-gauge Tuohy and 27-gauge atraumatic spinal needles was used. The inadvertent dural tap rate was 1%. There was a 10.6% failure rate in obtaining CSF with the long 27-gauge atraumatic needle. This was partly because all 300 women were in the left lateral position during insertion of the combined spinal–extradural. Norris and colleagues[4] found that they were significantly more likely to obtain CSF in the sitting than in the lateral position. Sagging of the midline skin crease and reduced hydrostatic pressure head of CSF in this position may conspire to increase the likelihood of a dry tap. Furthermore, trainees with varying levels of competence and experience in any form of obstetric regional block performed all blocks in the Queen Charlotte's Hospital study. To increase the chances of obtaining CSF, multiple deliberate dural punctures with the spinal needle were used, accounting for the excess incidence of PDPH over and above the observed inadvertent Tuohy tap rate of 1%.

As experience with the combined spinal–extradural technique increased in this unit, Morgan and Kadim[7] were able to report that in the next 1565 women who received combined spinal–extradural analgesia, inadvertent dural tap rate had decreased to 0.45% and the incidence of PDPH as a result of deliberate dural puncture with a 27-gauge atraumatic spinal needle had decreased to 0.13% from 1.3%; failure to obtain CSF occurred in only 5.3% of cases.

The study by Norris and colleagues[4] reported an apparently lower incidence of inadvertent dural puncture in women who had combined spinal–extradural analgesia rather than extradural analgesia in labour (notwithstanding that their overall inadvertent dural tap rate was 2.7%). However, that particular unit reserves extradural analgesia for later in labour and combined spinal–extradural analgesia for those who request regional analgesia earlier in labour. As distressed parturients in later labour are more likely to be moving targets than women in early labour, it is not surprising that the inadvertent dural tap rate is higher in this group. This would presumably be the case even if they received combined spinal–extradural analgesia rather than extradural only analgesia.

There is no conclusive evidence that combined spinal–extradural analgesia in labour is associated with an excessive incidence of PDPH. But it would seem preferable to restrict the use of combined spinal–extradural analgesia to those women who request regional analgesia in later labour (so as to benefit from the rapidity of onset of analgesia); those who require instrumental assisted delivery in the absence of a pre-existing regional block; and those who at any time in labour are excessively distressed (so as to rapidly achieve control of the situation).

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1. Jenkins JG. Ambulatory extradural analgesia in labour and mode of delivery. *British Journal of Anaesthesia* 1997; 78: 776–777.
2. Elton CD, May AE. Ambulatory extradural analgesia in labour and mode of delivery. *British Journal of Anaesthesia* 1997; 78: 777.
3. Collis RE, Baxandall ML, Srikantharajah ID, Edge GE, Kadim KY, Morgan BM. Combined spinal epidural analgesia: technique, management and outcome of 300 mothers. *International Journal of Obstetric Anesthesia* 1994; 3: 75–81.
4. Norris MC, Grieco WM, Borkowski M, Leighton BL, Arkoosh VA, Huffnagle HJ, Huffnagle S. Complications of labor analgesia: Epidural versus combined spinal epidural techniques. *Anesthesia and Analgesia* 1994; 79: 529–537.
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6. Brownridge P. Spinal anaesthesia in obstetrics. *British Journal of Anaesthesia* 1991; 67: 663.
7. Morgan BM, Kadim MY. Mobile regional analgesia in labour. *British Journal of Obstetrics and Gynaecology* 1994; 101: 839–841

Sir,—I thank Dr McLoughlin for his interest in my letter. The high rate (2.3%) of post-dural puncture headache (PDPH) in the original series of 300 combined spinal–extradurals for analgesia in labour, reported by Collis and colleagues,[1] was the only published data available when we made our decision to use low-dose extradural alone rather than combined spinal–extradural analgesia. Subsequently, Morgan and Kadim[2] reported a much lower rate of PDPH after combined spinal–extradural analgesia for labour. Recently, cases of both aseptic[3,4] and bacterial[4,5] meningitis have occurred after combined spinal–extradural analgesia in obstetrics. I believe combined spinal–extradural techniques should be used with caution for analgesia in labour.

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1. Collis RE, Baxandall ML, Srikantharajah ID, Edge G, Kadim MY, Morgan BM. Combined spinal epidural analgesia with the ability to walk throughout labour. *Lancet* 1993; 341: 767–768.
2. Morgan BM, Kadim MY. Mobile regional analgesia in labour. *British Journal of Obstetrics and Gynaecology* 1994; 101: 839–841.
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4. Harding SA, Collis RE, Morgan BM. Meningitis after combined spinal–extradural anaesthesia in obstetrics. *British Journal of Anaesthesia* 1994; 73: 545–547.
5. Aldebert S, Sleth JC. Meningite bacterienne apres anesthesie rachidienne et peridurale combinee en obstetrique (Bacterial meningitis after combined spinal and epidural anaesthesia in obstetrics). *Annales Francaises d'Anesthesie et de Reanimation* 1996; 15: 687–688.

Sir,—We agree that the evidence that combined spinal–extradural analgesia increases the incidence of post-dural puncture headache (PDPH) is conflicting. This expands the assertion in our original letter.[1] Combined spinal–extradural analgesia has proved extremely popular in centres in which it has been introduced, including Queen Charlotte's Hospital.[2] It has been suggested that conventional extradurals with bolus doses of plain bupivacaine are associated with increased operative[3] and instrumental delivery and long-term backache.[4] It is possible that combined spinal–extradural analgesia in labour has a different profile of side effects.[5]

It would be prudent to await the results of large scale, randomized controlled studies with long-term follow-up to establish the role of combined spinal–extradural analgesia in labour. We agree that where it is necessary to achieve rapid onset of profound analgesia, particularly where pain is of sacral origin, combined spinal–extradural analgesia has advantages.[6] However, the fact that anaesthetists at Queen Charlotte's Hospital experienced a greater incidence of side effects when combined spinal–extradural analgesia was introduced compared with subsequent studies[3] would imply that the use of an unfamiliar technique in such fraught situations may not be desirable.

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1. Elton CD, May AE. Ambulatory extradural analgesia in labour and mode of delivery. *British Journal of Anaesthesia* 1997; 78: 777.
2. Morgan BM, Kadim MY. Mobile regional analgesia in labour. *British Journal of Obstetrics and Gynaecology* 1994; 101: 839–841.
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4. MacArthur C, Lewis M, Knox EG, Crawford JS. Epidural anaesthesia and long-term backache after childbirth. *British Medical Journal* 1990; 301: 9–12.
5. May AE, Elton CD. Ambulatory extradural analgesia in labour reduces the risk of Caesarean section. *British Journal of Anaesthesia* 1996; 77: 692–693.
6. Stacey RGW, Watt S, Kadim MY, Morgan BM. Single space combined spinal–extradural technique for analgesia in late labour. 1993; 71: 499–502.

Transposition of rotameter tubes

Sir,—With the publication of the new checklist for anaesthetic apparatus from the Association of Anaesthetists,[1] we feel that the incident reported in this letter will highlight the importance of these checks. However, in addition, having read carefully this document we can find no instruction which would ensure that the fault we describe would be detected in the future.

There were two reports of a rotameter and a bobbin swap from the USA in 1974.[2,3] However, there has previously been no report in this country of such an incident. But the morning after an anaesthetic machine service in this hospital, a full check of the anaesthetic machines in the anaesthetic room and operating theatre was made according to the guidelines of the Association of Anaesthetists of Great Britain and Ireland (AAGBI)[4] by the anaesthetist who was working in that theatre. Nothing untoward was noted at this time. Anaesthesia was carried out safely in the first patient in the anaesthetic room before transfer to theatre. As soon as the anaesthetist turned on the gas flows on the machine in the operating theatre he realized that the flowmeter above the nitrous oxide flow control valve was only calibrated to 2 litre. On closer inspection, this flowmeter was noted to be colour coded and labelled for carbon dioxide. The flowmeter above the carbon dioxide flow control valve was conversely colour coded and labelled for nitrous oxide (fig. 1). The anaesthetist administered 100% oxygen and a volatile agent to the patient while the anaesthetic machine was changed. The patient came to no harm.

How did the flowmeters get swapped? It is standard practice for the service engineer to remove, clean and replace each flowmeter in turn. On this occasion one of the flowmeters was broken on cleaning and then the next was removed, cleaned and replaced before a replacement for the broken one was found. This led to the swap.

Why was this swap not detected during the anaesthetic machine check? The checklist for anaesthetic machines[4] states to "set a flow of approximately 5 litre min^{-1}" for the flowmeters. The new trainee anaesthetist knows that this is approximately 50–66% up the oxygen and nitrous oxide flowmeter, without reading the scales. Therefore, the flowmeters were not read accurately to 5 litre during this check. Extra vigilance is needed in checking the anaesthetic machine to exclude a crossover of flowmeters after a machine service. How might such a potentially serious fault be avoided in future? Flowmeter design could be changed so that it would not be possible for them to be interchanged. Clearly the procedures being followed by the service engineer were not foolproof. Perhaps after each anaesthetic machine service the

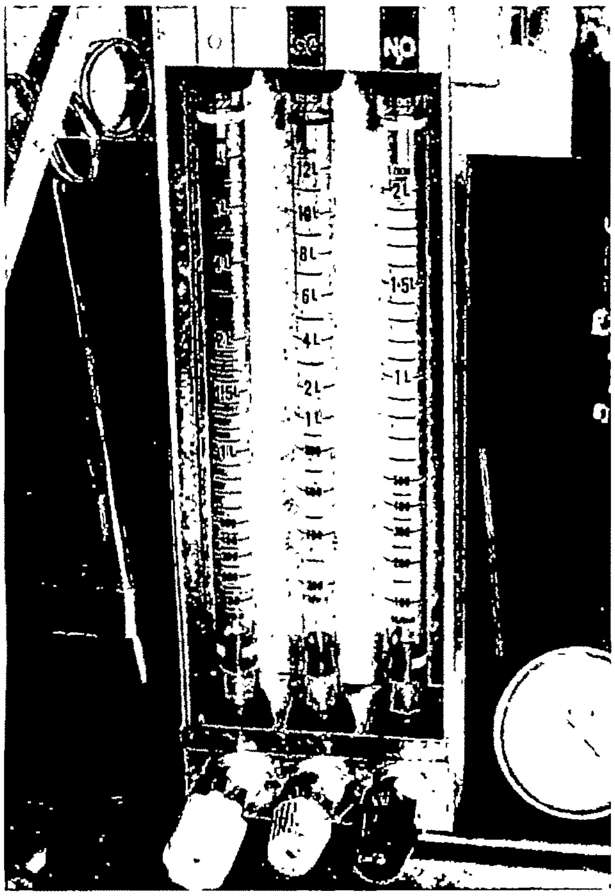

Figure 1 Flowmeters of the anaesthetic machine.

machine should be double checked by an independent technician. A much more comprehensive checklist than the one currently described by the AAGBI is possibly required after a machine service. Currently, we reinforce to our trainees that they must set the bobbin height to exactly 5 litre when doing their anaesthetic machine checks to guarantee that the flowmeter calibrations are read accurately.

The second question to be asked is what difference to the outlet gas mixture would a switch of this sort make? The two possibilities are of an hypoxic mixture (picked up by the oxygen analyser) or an oxygen-enriched gas mixture leading to the possibility of awareness. Afterwards, oxygen and nitrous oxide concentrations from the faulty machine were measured, setting both flowmeters to read 2 litre as this was the maximum the "nitrous oxide" flowmeter could read. Equal concentrations of each gas were emerging from the common gas outlet. If the flowmeters are calibrated for individual gases, why was the flow of nitrous oxide through a carbon dioxide flowmeter accurate? With the bobbin type of flowmeter, the physical property determining flow is gas viscosity at low flow rates and gas density at high flow rates. The viscosities of carbon dioxide and nitrous oxide are 13.9 and 13.5 Pa.s, respectively. The density of both is 1.98 kg m^{-3}.

In summary, although service procedures are set and followed by companies, mistakes can occur. No checklist can ever be foolproof. Extra vigilance in checking anaesthetic machines is strongly recommended, particularly after servicing. The importance of following the AAGBI checklist for anaesthetic apparatus[1] cannot be overemphasized. However, a more comprehensive checklist may be required after an anaesthetic machine service.

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1. Checklist for anaesthetic apparatus. London: Association of Anaesthetists of Great Britain and Ireland, 1997.
2. Chadwick DA. Transposition of rotameter tubes. *Anesthesiology* 1974; 40: 102
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4. Checklist for anaesthetic machines. London: Association of Anaesthetists of Great Britain and Ireland, 1990

Effect of hydroxyethyl starch on coagulation is difficult to assess *in vitro*

Sir,—We have read with interest the *in vitro* studies carried out by Egli and colleagues on the effect of haemodilution with hydroxyethyl starch (HES), gelatin and albumin on blood coagulation.[1] However, we cannot agree completely with the conclusion that HES compromises blood coagulation more than other substances because *in vitro* studies of the effect of HES on blood coagulation are, unfortunately, of limited value.

HES leads to coagulation disorders, particularly through impairment of factor VIII/von Willebrand factor. In 1985, Stump and colleagues[2] were able to show that this effect only occurs *in vivo*, not *in vitro*. They speculated that the reason for this could be either reduced release or impairment of the synthesis of factor VIII/von Willebrand factor. Our own studies support the hypothesis that accelerated elimination of factor VIII/von Willebrand factor is the cause for the observed coagulation disorders.[3] It is difficult, therefore, to simulate through *in vitro* studies the complex interaction of HES with the clotting system and in particular elimination via the reticuloendothelial system.

These difficulties are enhanced by the fact that the chemical composition of HES changes markedly *in vivo*. In recent studies, we were able to show that HES is metabolized *in vivo* in complex ways,[4 5] and that impairment of factor VIII/von Willebrand factor depends exclusively on the *in vivo* molecular weight of HES. This explains why haemorrhagic complications have almost exclusively been observed with high and medium molecular weight HES, which is not easily metabolized by the body, resulting in high *in vivo* molecular weights of the HES molecules HES with a medium or low molecular weight which is easily metabolized does not lead to a reduction in factor VIII/von Willebrand factor beyond the dilution effect, and rarely leads to haemorrhagic complications.[6] *In vitro* studies do not take into account this new finding, because HES is not metabolized *in vitro*, resulting in unrealistically high molecular weights of the starch molecules which are not observed *in vivo*.

Nevertheless, we believe that the experimental model of Egli and colleagues is innovative and interesting, particularly as the pathological mechanism of impairment of the clotting system through HES and the mechanism of the reduction in factor VIII/von Willebrand factor have not yet been elucidated. Future *in vitro* studies that incorporate the recent results should be able to yield interesting new insights.

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Sir,—Drs Grauer and Treib were concerned that the *in vitro* finding of an exaggerated effect on blood coagulation of hydroxyethyl starch (200 000/0.5) (HES) compared with gelatin and albumin solutions[1] would not be completely applicable to the *in vivo* situation. This concern was based on two findings: first, an apparent lack of a decrease of factor VIII/von Willebrand *in vitro* with impairment of blood coagulation[2]; and second, on the observation that the mean *in vivo* molecular weight of HES decreased during long-term haemodilution in the treatment of cerebrovascular disease with an associated decrease in blood coagulation.[3]

Stump and colleagues described stable VIII/von Willebrand factors in their *in vitro* experiments assessing mixtures of HES and plasma.[2] These results were achieved in citrated plasma to prevent clotting. Interestingly, when blood coagulation is not inhibited, as in our study using thrombelastography, HES and dextran solutions may precipitate coagulation factors such as factor VIII/von Willebrand *in vitro* also.[4] The effect of HES in decreasing factor VIII/von Willebrand thus would not have been missed in our *in vitro* studies. In addition, if we were only able to partially detect the effect of a decrease in factor VIII/von Willebrand in our *in vitro* study, we would have underestimated the *in vivo* difference between the blood coagulation effect of HES compared with albumin and gelatin solutions. Thus we cannot agree with the concerns of Grauer and Treib that our results would not substantiate a more exaggerated effect on blood coagulation of HES than albumin or gelatin solutions.

Treib, Haass and Pindur have recently suggested an interesting new concept to predict the effect of long-term haemodilution therapy using various types of HES on blood coagulation.[3] In patients treated for cerebrovascular disease, they found that the mean molecular weight of HES solutions decreased after infusion *in vivo* and that the effect on blood coagulation of these different HES solutions was better related to the mean *in vivo* molecular weight measured after 5–10 days than to the mean *in vitro* molecular weight (i.e. the mean molecular weight of the HES solution in the bottle before infusion).[3] During surgery, however, HES is administered for relatively short periods of time according to surgical blood loss and the volume replacement requirements of the patient. Thus additional HES solution of the original *in vitro* molecular weight is infused continually and therefore HES molecules with a molecular weight similar to *in vitro* molecular weight exert their effect on blood coagulation. The concept of the (long-term) *in vivo* molecular weight of a particular HES solution affecting blood coagulation is of limited clinical relevance for the intraoperative and early postoperative period.

In vitro testing of the effect of various volume expanders on blood coagulation using thrombelastography is considered adequate. Nevertheless, *in vitro* findings have to be confirmed *in vivo* before final conclusions regarding clinical management can be deduced.

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Haemostatic changes during total knee arthroplasty with different anaesthetics

Sir,—The study by Sharrock and colleagues[1] on haemostatic changes in total knee arthroplasty with different anaesthetic techniques reflects the continuing search for a better understanding of the mechanisms of postoperative deep vein thrombosis in major joint arthroplasty. There are three comments I would like to make.

While they are partially correct in their discussion that in total hip arthroplasty we did not confirm using spinal anaesthesia Modig and colleagues' findings of suppressed fibrinolysis with extradural block,[2] this was largely a reflection of haematological methodology. There were demonstrable differences between general anaesthesia and spinal anaesthesia in some measured haemostatic variables.[3] When comparing spinal anaesthesia with general anaesthesia in the immediate perioperative period, platelet count did not increase to the same extent, thrombin generation index (a measure of activation of coagulation) and factor VIIIRAg did not increase and there was less activation of fibrinolysis (as demonstrated by euglobulin clot lysis time).

These changes were consistent with suppression of the neuroendocrine response to surgery with spinal anaesthesia, as demonstrated by changes in plasma concentrations of cortisol in our patients[4] and were similar in the general anaesthesia group to those seen with exercise and exogenous infusions of epinephrine.[5 6] In our study, no exogenous catecholamines were used and it is possible that any differences between general and extradural anaesthesia in the study of Sharrock and colleagues were hidden by the use of epinephrine in the extradural local anaesthetic solution and i.v. ephedrine for cardiovascular control.

With respect to their comments on limb blood flow, based on our impedance plethysmography study during hip arthroplasty,[7] the enhanced blood flow seen in the surgical limb after relocation of the prosthesis and into the postoperative period with spinal anaesthesia compared with general anaesthesia may not necessarily apply to knee arthroplasty. In the latter case, maximal vasodilatation would be expected in the exsanguinated limb after tourniquet release, at least initially, irrespective of the anaesthetic technique used. It will be difficult to follow through this hypothesis with flow studies on patients undergoing knee arthroplasty.

Given the New York group's very large clinical experience in knee arthroplasty, I would be interested in their views on correct exsanguination of the limb before tourniquet inflation and its importance for the occurrence of deep vein thrombosis. Not all orthopaedic surgeons use a compression Esmarch bandage, and when they do so it is not always applied efficiently. This could well influence coagulation–fibrinolysis changes in the surgical limb.

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Sir,—We appreciate Dr Davis' comments on our article, as he was perhaps the first person to highlight the role of regional anaesthesia in the genesis of venous thrombosis.[1]

The first question relates to his observation of increased thrombin generation during operation and decreased fibrinolysis after operation in patients receiving general anaesthesia during total hip replacement (THR).[2] We noted no increase in thrombin generation (measured by thrombin–antithrombin complexes) or in the effect of thrombin formed (fibrinopeptide A), nor did we note any difference in fibrinolysis, although our study did not extend into the postoperative period. These differences most likely reflect the different operations and possibly the differences in blood loss between spinal and general anaesthesia during THR. There is no effect of anaesthetic technique on blood loss with total knee replacement (TKR).

The issue of the use of catecholamines during anaesthesia is an important point. Although epinephrine and exercise increase fibrinolysis in young people, we were unable to detect any augmentation during THR in elderly patients.[3] In contrast, we have noted that infusions of epinephrine are associated with less thrombogenicity during TKR performed with a tourniquet.[4] These are preliminary observations and whether or not this represents a suppressant effect of epinephrine on coagulation or a vascular effect is unclear.

With a tourniquet, there is little opportunity for extradural anaesthesia to augment flow in the operative limb and thereby alter venous thrombotic tendencies This was one of the reasons we chose to study TKR, as flow should not be a confounding variable. As we were unable to see any difference in fibrinolysis or markers of thrombin generation in our patients, we hypothesized that augmentation of flow after surgery may account for the decreased rate of deep vein thrombosis (DVT) noted with extradural anaesthesia after TKR. Whether or not this is true is unknown.

The final point relates to how well the leg is exsanguinated before tourniquet inflation. I suspect this is a significant determinant of the degree of venous thrombosis. Any blood remaining in the leg will be static and a potential nidus for DVT. For this reason, our surgeons assiduously attempt to exsanguinate the leg with an Esmarch bandage before inflating the tourniquet. However, to the best of my knowledge, this has not been studied.

I thank Dr Davis for his comments, as a fuller understanding of factors contributing to intraoperative thrombosis will help reduce morbidity after surgery.

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Extradural anaesthesia in elective Caesarean section

Sir,—We read with interest the article by Morton and colleagues[1] and would like to raise several points. First, we were concerned that the results of nine women from a study containing only 38 women were not valid for analysis of efficacy or pharmacokinetics, or both. This is a drop out rate of approximately 25%. Second, one patient who apparently had sensory block to T6 after receiving 0.75% ropivacaine 20 ml and increments of 2% lidocaine had spinal anaesthesia for Caesarean section because surgery was delayed. Analysis of table 3 shows that in this patient, surgery started 114 min after extradural injection. Analysis of table 2 shows that the median duration of sensory block at T6 was 3.4 h (range 1.3–5.8 h). Although the results of this patient were not included in table 2, this patient should still have had a significant sensory block. Why was this patient then given a spinal anaesthetic? If the height of the sensory block had receded it could easily have been extended by injecting more local anaesthetic via the extradural catheter. Furthermore, there are several reports in the literature where very high or total spinal blocks have occurred when spinal anaesthesia has been performed after extradural anaesthesia.[2-4]

Third, two mothers received accidental i.v. injection of ropivacaine 75 mg and 150 mg, respectively. The second of these patients developed mild signs of i.v. injection after a dose of 75 mg but symptoms resolved, and therefore the authors gave another 75 mg at which time the symptoms recurred. Surely the authors should have stopped injecting after the initial 75 mg, aspirated the extradural catheter and waited a few minutes to see if any signs of sympathetic, sensory or motor block developed. If no signs of extradural block had developed the catheter should have been assumed to have been placed i.v. Furthermore, were there any signs of i.v. catheterization at the time of siting and were the catheters aspirated before injecting the test dose? It is fortunate that the study was not double-blind with bupivacaine!

Fourth, the authors failed to mention which form of anaesthetic was administered to the mother who received ropivacaine 150 mg i.v. The authors did not give the results of neonatal outcome in the two mothers who had accidental i.v. injection. Were their NACS scores normal?

Finally, as the authors mentioned in their discussion, the open design of the study had limitations, namely it prevented true comparisons with other agents or even with 0.5% ropivacaine. The conclusions of the study were somewhat predictable in that 0.75% ropivacaine should provide better analgesia compared with 0.5% ropivacaine or bupivacaine.[5] However, what is interesting is that 21 of 31 neonates in this study had a 2-h NACS score of less than 35 while in the study of Griffin and Reynolds,[5] where 0.5% ropivacaine was used, only five of 31 neonates had a 2-h NACS score of less than 35.

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Sir,—We thank Drs Patel and Baxter for their interest in our article. The reasons for the results from seven women being invalid for efficacy analysis were technical difficulty in siting the extradural catheter or failure to establish sensory block. Blood samples from another two women (with satisfactory extradural blocks) were not available for analysis for reasons stated in the article. Many authors do not report the fate of patients who are excluded from a study after recruitment (i.e. after giving informed consent) but we believe it is good scientific practice to do so. Furthermore, because ropivacaine was then an unlicensed drug, we felt it important to report the results from all patients who received it, including four of the above seven patients.

Drs Patel and Baxter question our choice of subarachnoid anaesthesia for the woman whose Caesarean section was delayed, inferring from the pooled data that she should either have had adequate block or block could have been extended. First, a median duration of sensory block at T6 of 3.4 h does not imply that this patient's block would have been adequate at the time of surgery. Second, we do not agree that her block could have easily been extended. The reason that she had received additional local anaesthetic was because of inadequate block. In addition, we were concerned about the possibility of systemic local anaesthetic toxicity. We are aware of the reports of high block when subarachnoid anaesthesia is used after inadequate extradural block but felt that the balance of risks still favoured this technique.

The second of the two mothers who received accidental i.v. injections of ropivacaine underwent Caesarean section under subarachnoid block. She received 0.75% ropivacaine 20 ml because her symptoms (not signs) were inconclusive. The injection was given slowly, which we believe is vital for safety, and therefore even if bupivacaine had been used, warning symptoms should have occurred before serious systemic toxicity developed. All extradural catheters were placed and all clinical decisions made by the consultant in charge of the patient's anaesthetic care. This person was not the investigator. As stated in the article, all catheters were aspirated.

NAC scores at 2 h and 24 h for the two women who received accidental i.v. injections were 30, 31 and 33, 36, respectively. None of the neonates in the study gave clinical cause for concern except that, as discussed in the article, one developed transient tachypnoea of the newborn.

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The expanding role of simulators in risk management

Sir,—We read with interest the recent correspondence by Dr Byrne and Professor Jones[1] in response to Professor Spences' editorial[2] on the expanding role of simulators in risk management. We are also aware of the excellent work that is being done with the ACCESS simulator.

We admit that we are fortunate in Bristol to have acquired one of the two commercially available American high-fidelity simulators. The METI version that we purchased cost approximately $200 000. The rest of the project money was used to house the simulator in a purpose-built education centre with additional computer-assisted learning (CAL) and conference facilities. The METI high-fidelity simulator can be used by single-handed operators for individual or group tutorial style teaching. It can also be used for the more glamorous scenario-based "anaesthesia crisis resource management" training. It is true that this type of training is time consuming, requires many trainers and benefits only a few trainees at a time.

In Bristol, we are encouraging the involvement of committed medical teachers (not just anaesthetists) to use our centre. Medical students and trainee anaesthetists attend the centre for tuition on a regular basis. Geographical location does mean that those in the South West of England are more likely to benefit from informal teaching programmes but we hope the commercial courses will appeal to many around the country. The manikin is immobile at present but it is our intent that teaching and training by simulation be available to a wider audience in the future. Pilot projects in the USA involve moving the simulator from one hospital base to another. This is potentially damaging to expensive equipment but mobile units may be available in the future. Alternatively, telemedicine links may provide opportunities for simulation teaching to a wider audience.

If high-fidelity simulators are to be used for trainee assessment and continuing medical education in the future, several points need to be considered. First, access to simulator facilities will need to be readily available. Second, trainers using simulators will need to cooperate and develop teaching and assessment programmes together, and third, the benefits of simulation as a teaching tool or in improving clinical performance need to be validated.

We are sure that the future success and developments of simulation lies in the collaborative efforts of those working in this exciting field of education.

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BOOK REVIEWS

Anesthesia for Aortic Surgery. J. I. Simpson (editor). Published by Butterworth–Heineman, Oxford. Pp. 394; indexed; illustrated. Price £55.00.

This book attempts to bring together, in a single volume, anaesthesia for those aortic procedures normally covered by a range of different subspecialties, such as cardiac, thoracic, paediatric and vascular surgery. The 21 contributing authors work in US centres, with one exception. The book is comprised of 13 chapters covering preoperative, intraoperative and postoperative care of these patients. There is some overlap, mainly with some of the anatomical discussions, with classification of aneurysms and with monitoring.

The first five chapters cover anatomy, preoperative risk assessment, radiological evaluation, monitoring, and bleeding and transfusion. Preoperative risk assessment covers predominantly coronary artery disease, but pulmonary and renal disease together with hypertension and diabetes are also included. With respect to haemodynamic optimization, the discussion is more typical of American practice, particularly the assumption that preoperative intensive care is available. However, the authors admit that its value is disputed. The chapter on radiological evaluation is informative and, as one would expect, well illustrated.

I particularly enjoyed the section on monitoring. It included discussion of the advantages and disadvantages of transoesophageal echocardiography in detecting wall motion abnormalities and the use of pulmonary artery catheters to monitor ischaemia and filling pressures. The discussion on measurement of cardiac contractility makes excellent reading. There is also an important discussion on the relative merits of central venous pressure monitoring compared with pulmonary artery catheter monitoring. This chapter also includes consideration of monitoring of brain and spinal cord function, with excellent contributions on the use of somatosensory evoked potentials and motor evoked potentials. The role of the EEG in deep hypothermic circulatory arrest is also included.

The middle chapters of the book cover the specifics of particular surgical procedures, divided into the ascending arch and descending aorta, together with chapters on anaesthesia for coarctation and the abdominal aorta. All of these chapters make good reading. Where appropriate they include sections on presentation, cerebral protection (including retrograde cerebral perfusion and the use and effects of hypothermia), alpha stat compared with pH stat management of arterial blood-gas tensions, and prevention of spinal cord ischaemia (including selective spinal cord cooling).

The latter part of this book covers postoperative care. Cardiopulmonary care is particularly well discussed, although I felt that perhaps there was too much discussion on the benefits or otherwise of "supranormal" oxygen delivery. However, many recent and highly relevant references are included. This section also included comment on the transfer of patients from the operating theatre to the intensive care unit, an area which sadly is often overlooked.

An entire chapter is devoted to the postoperative care of other "end organs", and including the central nervous system, renal function, coagulation and transfusion, and the gastrointestinal system. The latter discussion is particularly good but is marred by a poorly reproduced figure. The final chapter is devoted to discussion of postoperative management of pain in the aortic surgery patient. This is an excellent chapter and in many respects could equally apply to many other branches of surgery. It covers the available techniques and the use of different opioid analgesics by different routes. However, diamorphine is not included in this discussion.

This book has a comprehensive index and is well referenced. Inevitably, however, very few of the references are later than 1994. The tables, photographs and figures are, with one or two exceptions, usually of a high standard.

Overall I enjoyed this book. However, there were some problems. Naturally American drug names are used but I do find it irritating that throughout, where American units of measurement are used there are no SI equivalent values given. This applies both in the tables and text. Most British readers will not have a problem with electrolytes expressed in milli-equivalents, but expression of creatinine, for example, in imperial units will probably be unfathomable! There was one other infringement which this reviewer found particularly disconcerting! The name of the Liverpool based guru of paediatric anaesthesia, Jackson Rees, was spelt incorrectly.

These criticisms aside, the true test of this book will be to see who buys it. I suspect that those post-fellowship trainees considering a career in the relevant specialties may find this book attractive. Whether or not they will be prepared to spend £55, remains to be seen.

R. Wenstone

Head Injury Pathophysiology and Management of Severe Closed Injury. P. Reilly and R. Bullock (editors). Published by Chapman and Hall Medical, London. Pp. 478; indexed; illustrated.

This textbook has 27 authors and two editors from Australia, the USA and the UK. Twenty-nine chapters form three sections: the injury, measuring and monitoring injury and treatment. There are many figures and well reproduced images of CT and MRI scans, with some colour illustrations of newer imaging methods. Mixing of experts from different continents works well and the sources and perspectives are truly international and avoid the parochialism so common in US textbooks. Throughout the text certain key phrases, or sentences, are marked in bold italics. Some readers may find this irritating but I found it helpful and appreciated having important points emphasized. The breadth of the text is ambitious, covering air bags to excitatory amino acids. This is not just a tome on how to manage head injuries, it also informs on who suffers from them, how we might prevent them, processes taking place in the brain and how these might be detected and modified. The index is comprehensive; I looked up neuromuscular blocking agents, ketamine, hypothermia and hyperbaric oxygen and found useful information on all of them.

New drug treatments for head injury are eagerly awaited by clinicians and these are well reviewed in a chapter on "Neuroprotection in head injury" with many recent references. The balance of topics within individual chapters reflects the authors' interests. The section on patient transfer deals exhaustively with aeromedical evacuation and only briefly mentions road ambulances. Nevertheless the key points are covered.

The chapter on outcome dealt thoroughly with the controversies surrounding testing for brain stem death and the differences between US and UK practice. However, to be useful as a reference for trainees learning how to do the tests, some illustrations and explanations of the pathways involved would also have been appropriate. The persistent vegetative state is also well covered.

I liked this book because it is well written and interesting. I strongly recommend it to departmental libraries and interested individuals.

J. R. Sneyd

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

Death in the dental chair: an avoidable catastrophe?

At present approximately 300 000 patients undergo general anaesthesia for minor dental procedures in the UK each year. Of these 300 000, approximately 2 die.[1] Anaesthesia most commonly consists of a mixture of oxygen, nitrous oxide and halothane and is administered in general dental practices, community dental surgeries and hospitals. Of the 26 patients who died in the course of a dental anaesthetic between 1984–1993 (information from the British Dental Association) more than 50% were children less than 16 yr of age. A previous mortality report[2] suggested that the precipitating causes were distributed equally between respiratory difficulty and sudden cardiovascular collapse. Recent data obtained from the coroners' reports of two patients in the latter group suggest that the typical course of events is that they suffer an unexpected cardiac arrest with no obvious precipitating factor. The cardiac arrest in both cases proved resistant to resuscitative measures and the post mortems did not provide evidence as to the cause of the cardiac arrest and the deaths went unexplained.

It has long been known that patients undergoing general anaesthesia for dental procedures suffer changes in heart rhythm.[3–6] Stimulation of the sympathoadrenal system via the fifth cranial nerve in the presence of halothane is considered to be a major factor in the production of these arrhythmias. Halothane is also known to slow conduction between the atria and bundles of His and slow conduction in the ventricles. It has been postulated that this mechanism may allow re-entrant activity[6] and hence produce arrhythmias. The incidence of arrhythmias in dental surgical patients anaesthetized with halothane varies between 18% and 75%. Ryder and Wright[4] compared the use of halothane and enflurane in dental anaesthesia and showed that the incidence of arrhythmias with halothane was 32%, whereas it was only 9.8% with enflurane. Cattermole and colleagues[5] compared isoflurane with halothane and found that the incidence of arrhythmias with isoflurane was only 14%, which was 38% lower than with halothane.

The nature of the arrhythmias differed depending on the volatile agent used; with enflurane and isoflurane there was a total absence of ventricular ectopic beats whereas with halothane they occurred frequently. Ventricular arrhythmias are generally thought to carry a higher risk than those that are supraventricular in origin as the former are more likely to progress to ventricular fibrillation.[7] However, halothane has remained the agent of choice for inhalation induction and maintenance of anaesthesia in dental patients as both enflurane and isoflurane are irritant and can cause excessive coughing, salivation and laryngospasm.

Several large scale studies[8–11] revealed that the commonest causes of cardiac arrest during anaesthesia are hypoxia as a result of ventilatory problems and "overdose" of anaesthetic agent, particularly when combined with hypovolaemia, post-induction hypotension and post-succinylcholine asystole. In most cases of cardiovascular collapse, patients had pre-existing disease and were undergoing major surgery. This contrasts sharply with dental out-patients who are healthy individuals undergoing relatively minor surgery where cardiac arrests have occurred without any obvious precipitating factor. The nature of the arrests in the children who died was also unusual. Paediatric cardiac arrests are characteristically asystolic,[12] whereas children having dental treatment who are anaesthetized using halothane are prone to ventricular arrhythmias,[3 4] some of which have proceeded to ventricular tachycardia. In one case described in the coroner's court, ventricular fibrillation occurred without any preceding change in normal rhythm. Unfortunately data on the incidence of cardiac arrest during anaesthesia for dental surgery are limited as only deaths are recorded.

The number of deaths associated with dental anaesthesia is decreasing. The first Coplans and Curson report[2] examined deaths in dentistry over the decade 1970–1979, and during this period more than 15 million anaesthetics were given with a total of 100 deaths. In the period 1980–1989, the number of deaths had decreased to 42.[13] However, it is suggested that the reduction in mortality was attributable largely to the decrease in the number of general anaesthetics administered rather than improved standards, although no information is available on the numbers of general anaesthetics given during this latter period.

Nevertheless, because of the ongoing mortality (another two highly publicized deaths), a working party led by Professor Poswillo[14] was set up in 1989 to examine the need for general anaesthesia and sedation in dentistry outside hospital, and to develop guidelines for their safe use. In addition, part of their assessment was to comment on the provision for resuscitation, and undergraduate and postgraduate training in general anaesthesia, sedation and resuscitation. The working party concluded that: where general anaesthetics are given, full monitoring equipment in the form of an ECG, pulse oximeter, non-invasive arterial pressure and a capnograph together with a defibrillator should be available; there should be both a dental and an anaesthetic assistant present; there should be a fully equipped recovery facility with adequately trained staff; everyone who administers anaesthetics for dental surgery should be able to formally manage an airway, establish i.v. access, correctly give drugs used in resuscitation and be able to use a defibrillator; and that there should be an increase in postgraduate training in anaesthesia, sedation and resuscitation. The Clinical Standards Advisory Group's report on dental general anaesthesia in 1995[1] confirmed that the majority of dental practices had carried out the recommendations in the Poswillo Report, particularly with reference to basic monitoring. Unfortunately, the improved standards of care do not seem to have had any affect on mortality. Patients are continuing to die (still approximately two per year).

This leaves the basic question unanswered of why healthy people have unexplained cardiac arrests and die? One possible answer is the high propensity to arrhythmias in dental patients when halothane is used. The popularity of halothane for general anaesthesia in dental outpatients has continued because of the absence of a suitable alternative. However, with the advent of the new volatile anaesthetic agent, sevoflurane, the use of halothane needs to be re-assessed.

Sevoflurane is a halogenated ether which is non-irritant, has a pleasant odour and a low blood-gas solubility; such properties make it ideally suited to inhalation induction and maintenance of general anaesthesia for minor dental surgery in both adults and children. More importantly, Paris and colleagues[15] found that the incidence of arrhythmias with sevoflurane was 26% whereas with halothane it was 62%. Interestingly they found that only 6% of patients suffered arrhythmias during the recovery period; this may be relevant for outcome as Coplans and Curson in 1982[2] found that more than 50% of dental deaths occurred during the recovery period. The type of arrhythmias also differed[15]; with sevoflurane the associated arrhythmias were predominantly supraventricular whereas with halothane a far greater number of the more sinister ventricular arrhythmias were seen.

Deaths associated with general anaesthesia are always difficult to accept, particularly when they occur in children and young people with no pre-existing disease. Despite the time and money spent in recent years to improve the quality of care, patients undergoing general anaesthesia for dental procedures continue to have seemingly unprovoked cardiac arrests. Halothane, with its high incidence of ventricular arrhythmias, may no longer be the volatile agent of choice in these circumstances. Sevoflurane is now widely available and has been shown to produce rapid and smooth loss of consciousness during inhalation induction, is easy to use during maintenance of anaesthesia and has good recovery characteristics for day-care procedures. In addition, sevoflurane is associated with fewer cardiac arrhythmias. It may be that by using sevoflurane in place of halothane, further unexplained cardiac arrests in patients undergoing minor dental surgery can be prevented.

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CLINICAL INVESTIGATIONS

Conscious awareness during general anaesthesia: patients' perceptions, emotions, cognition and reactions

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Summary

We interviewed 45 patients, who answered advertisements ($n = 21$) or were referred by colleagues ($n = 24$), about their experience of intraoperative awareness using a standardized questionnaire. Auditory perceptions, hearing sounds or voices were mentioned by all patients (45 of 45): 33 of 45 patients understood and recalled conversations; 21 of 45 patients had visual perceptions; 12 of 21 recognized things or faces; 29 of 45 patients felt being touched; three patients had the sensation of moderate pain; and eight patients were in severe pain. Patients' feelings were mostly related to paralysis (27 of 45), helplessness (28 of 45), anxiety and fear (22 of 45); 18 were in severe panic. All patients (45 of 45) recognized the situation as a real event: 22 of 45 patients experienced unpleasant after effects; 11 suffered from anxiety and nightmares; and three developed post-traumatic stress disorder syndrome and required medical treatment. Twenty of 45 patients were especially attentive to emotionally relevant remarks on their own person, their disease and the course of their operation. The accuracy of sensory perception indicates a very high level of cognitive performance of patients during intraoperative awareness. (*Br. J. Anaesth.* 1998; **80**: 133–139)

Keywords: anaesthesia, general; anaesthesia, depth; memory; psychological responses

The incidence of awareness during general anaesthesia that can be recalled explicitly after operation has been reported to be 0.5–2%.[1–9] Patients waking up during their anaesthetic are awake, in agony, intensely fearful but completely helpless, thinking that something must have gone terribly wrong. After operation, they recall all of the details of the procedure and the shock of this experience may cause post-traumatic stress disorder (PTSD).[9–11] Characteristic symptoms of PTSD involve re-experiencing the event, sleep disturbances with recurrent nightmares, avoidance of stimuli associated with the event, numbing of general responsiveness or increased arousal, anxiety and preoccupation with death, that in some cases require long-term medical and psychological support or treatment.[9 12]

Information on what patients perceive and recall of events during general anaesthesia is based mostly on case reports.[13–21] Most of these case reports relate to the patient's actual experience rather than patient reactions or after effects of awareness. Consequences of intraoperative awareness have been described only on the basis of small series of patients.[22–29] Only two studies analysed patients' feelings during, and patients' reactions to, awareness. Evans studied 27 patients with recall after anaesthesia having selected his patients by advertising in four British newspapers.[30] Bias of this sample cannot be excluded because advertisements select a disproportionate number of patients with a strong interest in their own medical history (so-called complainers). Therefore, Moerman, Bonke and Oosting investigated 26 patients with experiences of awareness during anaesthesia referred by colleagues of the anaesthesia department of a large university hospital.[31]

In this study we have investigated two groups of patients with experiences of awareness. One group was collected from advertisements in four German newspapers and the Internet. Patients in the second group were referred by colleagues of the anaesthesia departments of one large university hospital and two large community hospitals. The incidence, quality, intensity and accuracy of sensory perceptions, emotions and feelings, cognition and realization, reactions, consequences and after effects during and after intraoperative awareness was assessed within and between groups.

Patients and methods

After obtaining approval from the local Ethics Committee, two groups of patients with experience of awareness during general anaesthesia were collected. In group 1, patients answered advertisements placed in four German newspapers and on the Internet. The text of the advertisement was as follows: "For scientific research and documentation on the subject of 'awake during general anaesthesia?' the Department of Anaesthesia of Munich University and the Science Department of the German state television, section SDR, are looking for patients who woke up

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Table 1 Case reports, patient data, perceptions, feelings and sequelae

Patient No.	Time interval	Patients' data (sex, age, height, weight)	Operation	Perceptions during intraoperative awareness	Sequelae
Group 1					
1	13 yr	F, 31 yr, 160 cm, 80 kg	Dental surgery	Heard people talking: "Stop, she is waking up, she needs some more anaesthetic", saw silhouettes, no pain, no anxiety	None
2	12 yr	M, 26 yr, 194 cm, 85 kg	Operation of a funnel breast	Felt hands and arms during being positioned and heard voices say: "we won't get along this way, we have to lay him down"	None
3	20 yr	M, 63 yr, 169 cm, 84 kg	Total hip replacement	Heard voices and the sound of metal, saw silhouettes and felt that his leg was moved up and down, moderate pain, helpless, in panic, tried to alert someone	Exaggerated sensitivity to sounds for 1.5 yr
4	2 yr	F, 24 yr, 162 cm, 60 kg	Cholecystectomy	Heard voices, felt no pain, helpless and in panic, paralysed, tried to open eyes and to alert someone	None
5	21 yr	F, 63 yr, 163 cm, 55 kg	Nephrostomy	Heard voices and the sound of metal, unable to open eyes, no pain, no anxiety	None
6	4 yr	M, 47 yr, 176 cm, 140 kg	Arthroscopy knee	Heard a voice saying: "how can a man be so fat"	None
7	26 yr	F, 63 yr, 158 cm, 65 kg	Caesarean section	Felt skin incision and touch, unbearable pain, heard: "she moves, she is coughing", saw silhouettes, felt paralysed, helpless, in panic, tried to alert someone	Increased fear of future anaesthetics and operations
8	30 yr	F, 40 yr, 167 cm, 65 kg	Operation on external ear	Heard sounds and understood conversation, no pain, clear sight, tried to alert someone, felt paralysed	None
9	7 yr	F, 45 yr, 163 cm, 63 kg	Cardiac valve replacement	Heard the sound of metal and a voice saying: "the patient tries to move. He is waking up!" tried to move finger, felt paralysed, unable to open eyes, tried to talk, felt helpless, no fear, no pain	Nightmares, anxiety of being unable to open eyes, for instance, when driving a car
10	4 yr	F, 58 yr, 168 cm, 73 kg	Lower extremity fracture	Heard voices, felt skin incision and unbearable pain, saw silhouettes, unable to move, helpless, tried to alert someone	None
11	17 yr	F, 23 yr, 163 cm, 47 kg	Herniorrhaphy	Moved arm and heard voices saying: "she is awake, she needs more anaesthetic" no anxiety, no pain	Nightmares, could not stay in bed after waking up
12	2 yr	M, 55 yr, 198 cm, 90 kg	Parotid tumour	Heard voices talking about the patient's increase in blood pressure, no anxiety, no panic, no pain	None
13	2 yr	F, 46 yr, 161 cm, 95 kg	Operation of the cervical spinal column	Recalled conversation concerning her overweight: "how can a women be so fat ?" and other disgusting jokes about her body weight	Depression for several weeks
14	19 yr	M, 56 yr, 179 cm, 80 kg	Anal fissure	Heard voices and understood conversation about how he lay on the operation table	None
15	2 yr	F, 33 yr, 155 cm, 82 kg	Caesarean section (emergency)	Heard: "She is awake" saw silhouettes, unable to open eyes, felt unbearable pain, paralysed, helpless, in panic, tried to alert someone	Nightmares, increased fear of future anaesthetics and operations
16	5 yr	F, 55 yr, 159 cm, 59 kg	Multiple trauma (emergency)	Heard voices and conversation of medical staff, saw light, silhouettes, no pain	None
17	4 yr	F, 33 yr, 171 cm, 86 kg	Caesarean section (emergency)	Felt pain during skin incision, heard conversation: "What about the suction device?" Tried to move, felt paralysed, saw lights and silhouettes	Nightmares and sleep disturbances for 2 yr
18	20 yr	F, 44 yr, 164 cm, 77 kg	Abortion curettage	Heard sounds, saw light, no pain, felt paralysed, helpless, in panic	None
19	9 yr	M, 49 yr, 176 cm, 77 kg	Aortocoronary bypass (emergency)	Heard and recalled conversation during emergency defibrillation, felt the electrical shocks and heard a voice saying: "We won't get him", panic	Severe anxiety, post-traumatic stress disorder, psychotherapy
20	16 yr	F, 46 yr, 168 cm, 70 kg	Caesarean section (emergency)	Heard sounds and conversation, able to understand and recall conversation, no pain, heard the sound of the crying baby after delivery	None
21	5 yr	M, 55 yr, 174 cm, 75 kg	Aortocoronary bypass	Heard sounds, understood conversation, no pain, felt paralysed	Anxiety, depression unable to stay in his job as an electrician, post-traumatic stress disorder

Table 1 Case reports, patient data, perceptions, feelings and sequelae—*continued*

Patient No.	Time interval	Patients data (sex, age, height, weight)	Operation	Perceptions during intraoperative awareness	Sequelae
Group 2					
1	2 yr	F, 52 yr, 168 cm, 73 kg, (anaesthetist)	Abdominal hysterectomy, anaphylactic shock (emergency)	Heard the word: "You have to give epinephrine, realized the emergency situation, thinking this is no more routine management, guys you are in severe difficulties, but I am sure, that you are doing the right things, giving epinephrine", no anxiety, no pain	None
2	5 yr	F, 33 yr, 169 cm, 52 kg, (anaesthetist)	Excisional biopsy, breast tumour	High-dose fentanyl anaesthesia, awake during the whole surgical procedure, heard sounds and conversation, saw silhouettes and felt being touched during the operation, no pain, no anxiety	None
3	16 yr	F, 37 yr, 167 cm, 42 kg	Appendicectomy (emergency)	Heard sounds and voices: "Can we start with the operation now?" Tried to alert someone, felt paralysed, helpless, in panic, no pain,	Increased fear of future operations or anaesthetics
4	4 yr	M, 35 yr, 180 cm, 80 kg	Multiple trauma, laparatomy (emergency)	Heard voices, saw silhouettes, no pain, felt helpless and paralysed, in panic, thought: "Now I have to die", tried to alert someone	Fear to die
5	5 yr	F, 36 yr, 162 cm, 63 kg	Laparoscopic cholecystectomy	Painful feeling in the upper abdomen, tried to move, felt paralysed	None
6	1 yr	F, 34 yr, 170 cm, 70 kg	Thyroidectomy	Heard voices saying: "the tube is too big but, we do not have another", no pain	None
7	20 yr	M, 45 yr, 179 cm, 74 kg	Septorhinoplasty	Heard sounds, opened eyes, saw surgeon and light, felt pressure on his head, no pain	None
8	7 yr	F, 39 yr, 159 cm, 74 kg	Caesarean section (emergency)	Felt warm fluid flowing over her abdomen, tried to open eyes, fear of bleeding to death	Sleep disturbances, fear to die, post-traumatic stress disorder, psychotherapy
9	10 yr	M, 24 yr, 170 cm, 80 kg	Upper extremity fracture	Felt intratracheal tube, heard voices and conversation: "Now we can start with the operation", tried to open eyes, felt paralysed, no pain	None
10	6 month	M, 44 yr, 182 cm, 85 kg	Appendicectomy (emergency)	Heard voices, felt painful skin incision, paralysed, helpless, tried to alert someone	None
11	1 yr	F, 46 yr, 166 cm, 80 kg	Meniscectomy	Heard conversation: "We now take a photo and show it to her afterwards", felt hands touching her, helpless, paralysed, panic	None
12	10 yr	F, 60 yr, 174 cm, 93 kg	Laparatomy, peritonitis (emergency)	Heard surgeons saying: "Why do we always have to treat the complications of other medical centres? This woman is lost anyhow."	Anxiety, nightmares
13	1 yr	M, 43 yr, 180 cm, 86 kg	Dental surgery	Heard the surgeon saying something to the anaesthetist, saw the surgical gloves as a silhouette	None
14	21 yr	F, 30 yr, 172 cm, 58 kg	Tonsillectomy	Felt her mouth being opened, could understand conversation and recognised the surgeon, the medical staff and the operating theatre. Moderate pain	None
15	1 yr	M, 14 yr, 161 cm, 54 kg	Gastroscopy	Heard conversation, felt touch, felt suffocated and paralysed	None
16	8 yr	F, 34 yr, 175 cm, 68 kg	Caesarean section (emergency)	Felt being touched, tried to alert someone, felt paralysed, heard voices	None
17	6 yr	F, 34 yr, 165 cm, 79 kg	Appendicectomy	Heard the surgeon saying: "She needs some more anaesthetic, because she is a red haired nurse and everything is different and very special in her case."	None
18	8 yr	M, 50 yr, 181 cm, 80 kg	Aortocoronary bypass	Heard voices, saw lights and silhouettes	None
19	6 yr	F, 29 yr, 168 cm, 72 kg	Caesarean section (emergency)	Felt being touched, heard the sound of the crying baby	None
20	10 yr	F, 25 yr, 165 cm, 59 kg	Dental surgery	Opened eyes, saw the surgeon, who went to call for the anaesthetist, saying: "She needs some more anaesthetics "	None
21	11 yr	F, 38 yr, 172 cm, 80 kg	Appendicectomy (emergency)	Felt the tracheal tube and heard the surgeon saying: "The appendix is shortly before perforating."	None
22	2 month	F, 37 yr, 165 cm, 72 kg	Laparoscopic cholecystectomy	Felt the tracheal tube, felt helpless, anxious	None
23	4 month	F, 43 yr, 162 cm, 62 kg	Laparoscopy	Heard the voice of the anaesthetist, unable to open eyes	None
24	4 month	M, 64 yr, 172 cm, 68 kg	Cholecystectomy	Felt tracheal tube, heard voices	None

during surgery while the operation was going on. Your experience will be an important contribution to our work. Please contact us. Your replies will be regarded as confidential. Please reply to SDR, Science-Department 68028 Mannheim/Germany."

Patients in group 2 were referred by colleagues of the anaesthesia departments of a large university hospital (Institute for Anaesthesiology, Ludwig-Maximilians-University Munich, Klinikum Innenstadt) and two large community hospitals (Institute for Anaesthesiology, Klinikum Augsburg and Institute for Anaesthesiology, Klinikum Kaiserslautern) requesting that they refer all patients with experience of awareness regardless of when the experience had occurred or the anaesthesia had taken place.

All patients in the two groups were interviewed using our standardized questionnaire "Awareness during general anaesthesia". The questionnaire was subdivided into six sections: personal data, detailed description in own words, sensory perceptions, feelings and emotions, cognition and interpretations, reactions, consequences and after effects. The following data were collected.

(1) Personal data: patient's name and address, age, sex, height, body weight, date, place and type of surgery, and preoperative feelings of nervousness, anxiety and pain.
(2) In the second section, patients were allowed to give a detailed description in their own words of perceptions, feelings and thinking while being awake during the anaesthetic.
(3) Incidence, quality, intensity and accuracy of sensory perceptions within the different sense modalities. *Auditory modality*: loud, low, close, far away, identification of the direction of the sound source, recognition of sounds or voices, understanding of language and conversation. *Visual modality*: able to describe light, shades, silhouettes, clearly or everything looking hazy, able to recognize things or people, either isolated or within a visual context. *Tactile modality*: feeling of being touched, quality and localization of sensation. *Paralysis*: unable to move arms, legs, head, vocal cords or other sites. *Nociceptive modality*: feeling pain, intensity, ranging from none, moderate to severe (0, 1, 2), identification of painful body part.
(4) Feelings and emotions differentiated into helplessness, weakness, fear and panic, with intensity ranging from none, moderate to severe (0, 1, 2).
(5) Interpretation of the situation and cognition, interpretation as dream or reality, estimation of duration and whether patient is trying to alert anyone or make signs.
(6) Patients' reactions, consequences for daily life and after effects: anxiety, fears, nightmares with intensity ranging from none, moderate to severe (0, 1, 2). Other consequences for daily life such as re-experiencing the event, numbing of general responsiveness, increased arousal, loneliness and lack of confidence in future life. Changing of opinion on anaesthesia and surgery and fear of repetition or more fear of future anaesthetics or surgeries. Duration of symptoms and whether the symptoms required medical treatment or a PTSD syndrome developed.

The last question was whether the patient informed the anaesthetist, surgeon, ward staff, general practitioner, partner, family or friends and what was their reaction.

STATISTICAL ANALYSES

Data are presented as mean (SD). For differences between groups, groups were compared using the Mann–Whitney *U* or chi-square test. Subgroups of patients were compared using chi-square or Fisher's exact test (two-sided). Differences were considered significant if $P < 0.05$, after Bonferroni's correction for multiple comparisons.

Results

During an 8-month period, 45 patients were analysed; 21 patients replied to the advertisements (group 1) and 24 patients were referred from the three hospitals involved in the study (group 2). In total, 45 questionnaires of awareness during general anaesthesia were analysed.

In table 1, case reports, patient data, a short description of patients' perceptions and feelings, and postoperative sequelae are presented. The two groups were comparable in patient data, type of surgery, a wide range of incidence, quality, intensity and accuracy of perceptions, emotions, cognition, reactions and after effects. Details on patients (sex, age, weight, height, time interval between interview and anaesthesia), type of surgery, patients' descriptions of their experiences of awareness in keywords and postoperative sequelae are presented in table 1. Mean age of the patients was 41.7 (range 14–64) yr, mean body weight was 73.9 (47–140) kg and body height 169.75 (153–194) cm. Thirty patients were female and 15 male, and the time interval between the event and the interview was 9.6 yr (range 0.1–30 yr). Events occurred during anaesthesia for elective general abdominal (n=16), cardiothoracic (n=5), orthopaedic (n=6), gynaecological (n=4) or ear–nose–throat or dental surgery (n=7). Seven cases of awareness were observed during Caesarean section and 14 patients underwent emergency surgical procedures.

In table 2 the incidence, quality, intensity and accuracy of perceptions, emotions, cognition, reactions and after effects are presented for group 1, group 2 and for both groups combined.

SENSORY PERCEPTIONS WITHIN THE DIFFERENT SENSE MODALITIES

All patients (45 of 45) had auditory perceptions, hearing sounds or voices. The sound source was described as loud in 28 of 45 and close in 29 of 45 patients; 33 of 45 patients understood and recalled conversations. Patients in group 1 heard the sounds louder and closer when being aware and were significantly more often able to understand conversations; 21 of 45 had visual perceptions, and 10 of these 21 described their vision as clear, while 10 patients saw only silhouettes. Twelve patients recognized things or faces and 10 were able to localize this in the visual context of the operating room. Twenty-nine patients felt being touched, 28 of these were able to localize exactly where they felt the touch. Thirty-four patients felt no pain, three patients felt moderate and eight patients severe pain. All patients with pain perceptions were able to localize exactly were they felt the pain. Twenty-seven patients had the feeling of paralysis, 22 of whom were able to localize the paralysed body parts.

EMOTIONS

Twenty-eight of 45 patients felt helpless, 22 of 45 had feelings of anxiety and fear, four had moderate fear and 18 were in severe panic.

COGNITION

All patients (45 of 45) recognized their situation as a real event. The estimated duration of the awareness episode during anaesthesia ranged from 1 to 60 min (mean duration 7.73 min). Thirty-one of 45 patients tried to alert someone or to make signs.

REACTIONS AND AFTER EFFECTS

Twenty-two of 45 patients suffered from after effects of their awareness episode; 21 changed their opinion on future anaesthetics and operations, 11 suffered from anxiety during the day and 11 suffered from nightmares. In nine patients the awareness episode had consequences for their daily life, three required medical treatment and three patients developed PTSD syndrome. The mean duration of after effects was 0.84 (range 0.1–5.0) yr. Patients in group 1 had nightmares more often and after effects lasted significantly longer compared with those in group 2. Forty of 45 patients informed the anaesthetist, surgeon, medical staff, family or friends after operation. The response appeared to be affirmative, ranging from sympathy and explanation (19 of 40), or defensive, ranging from disbelieve to denial (10 of 40).

We subdivided all patients into two groups and compared those patients with and without after effects. Almost all patients with after effects had changed their opinion on anaesthesia and surgery ($P = 0.001$). Patients with after effects were significantly more often helpless ($P = 0.001$) and in fear or severe panic ($P = 0.049$) when being aware during operation compared with patients without after effects. There was no difference between patients with and without after effects regarding incidence and intensity of pain perception ($P = 0.856$) and other sensory perceptions, emotions and cognition.

Discussion

The two patient groups (21 patients who answered the advertisement (group 1) and 24 patients referred by colleagues of the large hospitals (group 2)) were comparable in patient data, type of surgery, a wide range of perceptions, emotions and cognition during their awareness episode, and incidence of after effects. Differences were found only in the quality of auditory perception and the incidence of understanding of language. Patients in group 1 heard the sounds louder and closer and were significantly more

Table 2 Incidence, quality, intensity and accuracy of perceptions, emotions, cognition, reactions and after effects.*$P<0.05$;**$P<0.01$ (chi-square test)

	Group 1 *n* (%)	Group 2 *n* (%)	Group 1+2 *n* (%)
Auditory perception	21 (100.0)	24 (100.0)	45 (100.0)
Intensity loud**	17 (80.9)	11 (45.8)	28 (62.2)
Distance close*	18 (85.7)	11 (45.8)	29 (64.4)
Understanding language, recall conversation*	18 (85.7)	15 (62.5)	33 (73.3)
Visual perception	11 (52.4)	10 (41.7)	21 (46.7)
Quality of visual perception clear	5 (45.5)	5 (50.0)	10 (47.6)
Recognition of things, faces	6 (54.5)	6 (60.0)	12 (57.1)
within a visual context	4 (36.4)	6 (60.0)	10 (47.6)
Tactile perception	14 (66.7)	15 (62.5)	29 (64.4)
localisation of tactile perception	13 (92.9)	15 (100.0)	28 (96.6)
Pain perception moderate	1 (4.8)	2 (8.3)	3 (6.7)
Pain perception severe	6 (28.6)	2 (8.3)	8 (17.8)
localisation of pain	7 (100.0)	4 (100.0)	11 (100.0)
Paralysis	13 (61.9)	14 (58.3)	27 (60.0)
localisation of paralysis	11 (84.6)	11 (78.6)	22 (81.5)
Helplessness	13 (61.9)	15 (62.5)	28 (62.2)
Anxiety moderate	1 (4.8)	3 (12.5)	4 (8 9)
Anxiety severe panic	10 (47.6)	8 (33.3)	18 (40.0)
Recognition as real event	21 (100.0)	24 (100.0)	45 (100.0)
estimated duration of awareness (min) (mean (SD))	9.46 (6.08)	6.00 (13.1)	7.32 (14.17)
Tried to alert someone	16 (76.2)	15 (62 5)	31 (68.9)
After effects	11 (52.4)	11 (45.8)	22 (48.9)
Duration of after effects** (yr) (mean (SD))	1.59 (1.93)	0.08 (0.15)	
Changed opinion	10 (83.3)	11 (100.0)	21 (91.3)
Anxiety	6 (66.7)	5 (45.5)	11 (55.0)
Nightmares**	8 (80.0)	3 (27.3)	11 (52.4)
Consequences for daily life	7 (63.6)	2 (18.2)	9 (40.9)
Medical treatment	2 (18.2)	1 (10.0)	3 (14.3)
Post-traumatic stress disorder	2 (18.2)	1 (10.0)	3 (14.3)
Informed other people	19 (90.5)	21 (87.5)	40 (88.9)
Anaesthetist	10 (52.6)	13 (61.9)	23 (57.5)
Surgeon	12 (63.2)	7 (33.3)	19 (47.5)
Ward staff	7 (36.8)	5 (23.8)	12 (30.0)
General practitioner	4 (21.1)	2 (10.5)	6 (15.8)
Family/ friends	14 (77.8)	9 (45.0)	23 (60.5)
Response of other people affirmative (sympathy to explanation)	8 (42.1)	11 (52.4)	19 (47.5)
Response of other people defensive (disbelief to denial)	5 (26.3)	5 (23.8)	10 (25 0)
Response of other people no detail	6 (31.6)	5 (23.8)	11 (27.5)

often able to understand conversations. One important difference between groups was that group 1 patients had nightmares more often and after effects lasted significantly longer than in group 2 (mean duration 1.59 *vs* 0.08 yr). This may be because of a bias in patient collection, indicating that patients who answered the advertisements had severer and longer lasting postoperative sequelae and possibly a stronger interest in their own medical history (so-called complainers). Our data support the suggestion of Moerman, Bonke and Oosting that it cannot be excluded completely that by advertising, a patient sample is biased and a disproportionate number of "complainers" may be selected with a strong personal interest in their own medical history.[31]

As in the studies of Moerman, Bonke and Oosting[31] and Evans,[30] reports of awareness during anaesthesia in our analyses occurred not only during "high risk awareness" surgical procedures such as obstetric, cardiac or emergency surgery. The majority of awareness cases in our study occurred during elective ear, nose, throat, dental, general, abdominal, orthopaedic or gynaecological surgery, indicating that awareness during anaesthesia is not only a problem of special surgical procedures but may occur occasionally during anaesthesia for almost any elective procedure.

The incidence of perceptions within the different modalities during intraoperative awareness correspond well with data reported in the literature.[1,9,15,24,26,27,30,32] All patients were able to hear, indicating that the auditory modality is the most important sensory channel during intraoperative awareness. A high percentage of patients, especially those who heard loud sounds with the sound source close by, were able to understand language and remember conversations after operation. Twenty patients were especially attentive to emotionally relevant remarks, that is they recalled remarks on their own person, disease and course of the operation (two cases of derogatory remarks, two cases of very meaningful remarks and 15 cases of some type of meaningful remarks). This finding may support a widespread belief that meaningful words and remarks are recalled more easily than neutral sounds and have a greater impact on the patient.[25,28,29,33–36] On the other hand, 25 patients recalled only general theatre chat and noise.

Visual perception was reported by nearly 50% of our patients. This experience has been rarely documented and exceeds incidences reported by Moerman, Bonke and Oosting (27%) and Evans (33%). Furthermore, 50% of our patients with intraoperative visual perceptions had clear sight and could recognize things and faces within a clear visual context of their visual field. A high percentage of patients had tactile sensations and almost all were able to localize the body parts exactly where they were being touched. The high incidence of paralysis in our study corresponds well with data from the literature and in almost all cases the paralysed body parts could be identified.

The incidence of pain perception in our study (25%) was less than that reported in the literature (40%).[30,31] Nevertheless, 17.8% of patients had severe pain. All patients were able to localize the body part exactly where the painful stimuli occurred. Jones estimated the incidence of conscious awareness with pain to be lower than 1 in 3000 anaesthetics, and the incidence of conscious awareness without pain perception to be 1–3 in 300 anaesthetics.[9] This would imply that painful feelings occur in less than 10% of patients who are aware during anaesthesia. Our data and those of Moerman, Bonke and Oosting, and Evans exceed this estimate; this may be a result of the small sample size and the possible disproportionate number of "complainers" in our study.

Two-thirds of patients had emotional distress during their intraoperative awareness and felt helpless or anxious; 40% felt severe distress and panic, an incidence significantly lower than that reported by Moerman, Bonke and Oosting (92 %)[31] and Evans (78%).[30]

The percentage of patients who suffered after effects (50%) was slightly lower than in the study of Moerman, Bonke and Oosting.[31] Their symptoms corresponded with those reported in the literature.[9–12,22,28,37–40] Anxiety during the day, nightmares and sleep disturbances with consequences for daily life were most frequently mentioned. Most often, patients with after effects changed their opinion on anaesthesia and surgery with more fear for future procedures and that such an episode could happen again. Three patients required medical treatment after operation because of the development of PTSD. Why some patients experience after effects or develop PTSD and others do not cannot be explained from the present data. In contrast with Moerman, Bonke and Oosting,[31] we did not find a trend towards a correlation between intraoperative pain perception and the incidence of after effects in our patients. Nevertheless, our patients with after effects felt significantly more helpless, fearful or severe panic during operation than patients without after effects.

The percentage of patients who informed an anaesthetist, surgeon, hospital staff, family or friends (89%) was higher in our study than reported previously.[30,31] This may reflect the increasing popularity that the topic of awareness during anaesthesia has gained in the lay press within the past years and the growing general knowledge of such problems. In contrast with Moerman, Bonke and Oosting, and Evans, responses were mostly affirmative, ranging from sympathy to explanation of the event, although responses of disbelief and denial occurred in some cases. These observations may indicate a steadily increasing understanding of the phenomenon and problems of intraoperative awareness on the part of the patient in addition to anaesthetists and surgeons.

In summary, our data indicated a high accuracy of sensory perceptions, especially auditory perceptions, understanding and recall of conversations, and a high level of cognitive performance of patients during intraoperative awareness. The results illustrate the need for the anaesthetic and operating theatre staff to realize that awareness may be occurring during general anaesthesia.

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Preoperative assessment for difficult intubation in general and ENT surgery: predictive value of a clinical multivariate risk index†

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Summary

Several clinical multifactorial indexes have been described for predicting difficult laryngoscopy or intubation, or both, mostly in general surgery, and less frequently in ENT surgery. The objective of this study was to develop and validate a single clinical index for prediction of difficulty in tracheal intubation in both ENT and general surgery. We studied a population of 1200 consecutive ENT and general surgical patients. Clinical criteria were tested using univariate and multivariate analysis. Difficult intubation was defined as requiring unusual techniques. Logistic regression identified seven criteria as independent predictors of difficult tracheal intubation: previous history of difficult intubation; pathologies associated with difficult intubation; clinical symptoms of pathological airway; inter-incisor gap and mandible luxation; thyromental distance; head and neck movement; and Mallampati's modified test. Point values were assigned to each of these factors in proportion to regression coefficients representing the relative weight of each predictive intubation difficulty factor, the sum comprising the score. The best predictive threshold was chosen using a receiver operating characteristic curve. We then prospectively studied and validated the score in a population of 1090 consecutive ENT and general surgery patients. The sensitivity and specificity of the predictions were 94% and 96% in general surgery, 90% and 93% in non-cancer ENT surgery, and 92% and 66% in ENT cancer surgery, respectively. (*Br. J. Anaesth.* 1998; **80**: 140–146)

Keywords: Intubation tracheal, difficult; surgery, general; surgery, otolaryngological

Difficult tracheal intubation may increase anaesthetic morbidity and mortality, especially during obstetric[1 2] and other types of anaesthesia.[3 4] Several prospective studies have identified various individual clinical symptoms possessing a significant association with laryngoscopy or intubation difficulties.[5–13] Sensitivity and positive predictive values of these individual signs are low, ranging from 33% to 71% for sensitivity. Thus six studies have challenged multifactorial prediction indexes of difficult tracheal intubation or difficult view of the glottis, or both; five found a decrease in falsely predicted laryngoscopy or intubation difficulty,[14–18] whereas no improvement in sensitivity was found by Tse, Rimm and Hussain.[19] Another study[20] calculated the probability of difficult laryngoscopy using different combinations of predictive signs and a multivariate analysis; however, the optimal predicting level of these associations was not determined. Finally, comparison of these studies led to the conclusion that a multifactorial clinical index generally improves the prediction of difficult laryngoscopy or tracheal intubation.

Studies of multifactorial clinical index assessed predictions of difficult laryngoscopy in ENT and oral,[14] general[15 17–19] and gynaecological and obstetric populations.[16 20] To date, no single multifactorial index can be applied to the various surgical populations. Moreover, most, with the exception of Wilson's index, have not been validated prospectively.[17 21] However, Wilson's index is validated only for prediction of difficult laryngoscopy, as defined by Cormack and Lehane,[22] as inability to see the glottis in the standard intubation position. Finally, no index, including Wilson's, has been validated prospectively for detection of difficult tracheal intubation per se.

For these reasons, we undertook the development and validation of a predictive clinical multifactorial risk index, based on a multivariate analysis, aimed at predicting difficult tracheal intubation, both in general and ENT surgery.

Patients and methods

This prospective study was conducted in two steps. First, 12 different criteria, selected because of previously demonstrated statistical associations with difficult laryngoscopy or tracheal intubation, were recorded in a consecutive series of patients. Using a multivariate analysis, we then established a multifactorial clinical index to predict difficult tracheal intubation. In a second prospective step, this index was tested, and its performances evaluated in another series of patients.

INITIAL STUDY

During an 18-month period, any patient older than 15 yr of age undergoing ENT or general surgery

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with tracheal intubation was considered as potentially eligible for this prospective study. Five senior anaesthetists served as investigators and 1200 consecutive patients were included during this period based on the following factors recorded during preoperative consultation.

(1) Weight, height and age.

(2) Knowledge by the patient of previous difficulty with laryngoscopy or intubation, that is had the patient been informed previously of a difficulty during a previous operation in another medical centre.

(3) Pathologies associated with difficulties in laryngoscopy or intubation, such as malformation of the face,[23] acromegaly,[24] cervical spondylosis with limitation of neck movements,[6] occipito–atlanto–axial disease,[7] tumours of the airway and long-term diabetes mellitus with "stiff joint syndrome".[25–27]

(3) Clinical symptoms of airway pathology, such as dyspnoea related to compression of the airway, dysphonia, dysphagia and sleep apnoea syndrome[28 29] (this syndrome was considered either in the case of a previously fully documented illness or in the case of snoring associated with two other major symptoms among sudden arousal with choking, excessive day time sleepiness or unrefreshing sleep).

(4) Inter-incisor gap (IG) and mandible luxation (ML) evaluated using three levels: (i) IG <3.5 cm and negative ML; (ii) IG 3.5–5 cm and no ML; (iii) IG >5 cm or positive ML.

(5) Tooth morphology: buck teeth or normal teeth.

(6) Cervical morphology: short thick neck or normal neck.

(7) Thyromental distance measured with the head fully extended: < or >6.5 cm.

(8) Maximum range of the head and neck movement, measured as described by Wilson and colleagues[17]: the patient was asked to fully extend the head and neck while a pencil was placed vertically on the forehead. The orientation of the pencil was adjusted so that it was parallel to a distant window frame. Then, while the pencil was held firmly in position, the head and neck were fully flexed and the pencil was sighted against the horizontal of the window frame to judge if it had moved through 90°. This criterion was graded into three levels: < 80°; near 90° (90°±10°); > 100°.

(9) Mallampati's modified test[11] divided into four classes: class I = soft palate, fauces, uvula and pillars seen; class II = soft palate, fauces and uvula seen; class III = soft palate and base of uvula seen; and class IV = soft palate not visible.

The results of these factors were noted.

In the operating room, each patient was placed on the table with the head and neck in the optimal intubating position (sniffing position). The anaesthetist chose an anaesthetic induction technique according to the preoperative assessment, his own beliefs and any concomitant medical problems. General anaesthesia with neuromuscular block (vecuronium 0.1 mg kg^{-1}) was chosen by anaesthetists when they thought that intubation would be easy or when this mode of induction was thought to be the most appropriate for any other specific medical problem. When any difficulties were anticipated, a topical anaesthetic was used with gradual application of 5% lidocaine 120 mg from the lips to the glottis with 1% lidocaine 30 mg on the trachea using a spray (Abbott Laboratories, North Chicago IL, USA), accompanied by slight anaesthesia (midazolam 1 mg, fentanyl 50 µg and propofol 1 mg kg^{-1}) maintaining spontaneous breathing. Then, laryngoscopy was performed using a Macintosh blade and the glottic view was noted using Cormack and Lehane's classification[22]; intubation was then attempted. Adjuvant manoeuvres, such as external cricoid pressure or upward pressure on the epiglottis with the tip of the blade, or both, were also used. When the first attempt failed, a second was made using the large Miller blade and other manoeuvres. In case of failure, a second senior anaesthetist was required for further attempts using the same techniques and deepening anaesthesia if warranted. In case of failure by the second anaesthetist, intubation was said to be difficult and other special devices, not available routinely in every operation room, were considered. Thus intubation was defined as difficult when special techniques were required, as assessed by two senior anaesthetists. If their evaluation differed, intubation was not considered as difficult. The special techniques used in our department are: gum elastic bougies, fibreoptic intubation, the Piquet–Crinquette–Vilette's laryngoscope,[30] which is used mainly in France for ENT patients, and the Bullard laryngoscope.[31–33] Several other laryngoscopes are also available but were not used.

STATISTICAL ANALYSIS

The association between different variables and difficulty in intubation was evaluated using the chi-square test for qualitative data and the Student's t test for quantitative data. $P < 0.05$ was regarded as significant. Sensitivity, specificity, positive and negative predictive values were calculated according to standard formulae. Stepwise logistic regression analysis, using the SAS program, was performed with data from 1200 patients to identify multivariate independent predictors of difficult intubation. Variables in the predictor sets were found by a forward selection process such that introduction of additional variables was permitted only if P remained less than 0.05. Regression coefficients of each predicting factor in the final regression analysis were then used as "points", their sum giving "the exact score". These coefficients represent the relative weight of each predictive factor assessing difficult intubation. The discriminant function coefficient assigned to each statistically significant factor was then multiplied by a fixed value and rounded to the nearest whole number to derive a "point" value suitable for clinical purposes. Addition of these "point" values led to a simplified score.

SCORE VALIDATION STUDY

The effectiveness of this simplified score was tested subsequently by 17 senior anaesthetists in 1090 consecutive patients. The aim of this second series was to validate prospectively the simplified index and its optimal predictive level when used by several investigators. In this study, we calculated index performance in the prediction of difficult tracheal intubation. The same design was used as in previous studies.

Table 1 Number of patients undergoing different surgical procedures in the two studies (initial and validation studies)

Surgical population	Initial study (*n*)	Validation study (*n*)
ENT surgery		
Cancer	187	83
Non-cancer	425	290
General surgery		
Oral	312	421
Neurosurgery	102	
Abdominal	92	53
Gynaecology	29	53
Orthopaedic	28	32
Urology	25	88
Cardiac		70
Total	1200	1090

Results

INITIAL STUDY

As shown in table 1, among the 1200 patients included, 588 were undergoing general surgery; neurosurgical procedures were mainly lumbar slipped disc or intracranial lesions; orthopaedic operations were mainly joint prosthesis, without any atlanto–axoido–occipital joint surgery. A total of 425 patients were undergoing non-cancer ENT surgery, including 12 (2.8%) patients for sleep apnoea syndrome; 187 patients were undergoing ENT cancer surgery, including laryngectomy, pharyngectomy, glossectomy and endoscopy for diagnosis. For the whole population, in 50 patients (4.2%) the trachea was difficult to intubate: 12 (2.0%) undergoing general surgery, 15 (3.5%) ENT non-cancer surgery and 23 (12.3%) ENT cancer surgery. No intubation failed completely.

In tables 2 and 3, the number of difficult tracheal intubations is given according to Cormack and Lehane grades and mode of induction selected, respectively. There were no significant differences in weight or height between patients without difficult intubation (mean 67 (SD 13) kg and 168 (9) cm) and patients with difficult intubation (67 (12) kg and 169 (7) cm). Patients with a trachea difficult to intubate were older (50 (17–78) yr) than those with easier ones (43 (15–92) yr) ($P = 0.006$). Each of our qualitative criteria (airway pathology, clinical symptoms, etc.) showed a significant association with difficult intubation, after univariate analysis, except for tooth morphology. Univariate analysis identified nine factors, including age, with a significant association with difficult intubation (table 4).

Stepwise logistic regression analysis identified seven factors as independent predictors of difficult

Table 2 Characteristics of patients and difficult intubations according to glottic view (Cormack and Lehane grades) in the initial study

	Global population		General surgery		ENT non-cancer surgery		ENT cancer surgery	
	Intubation easy	Intubation difficult	Intubation easy	Intubation difficult	Intubation easy	Intubation difficult	Intubation easy	Intubation difficult
Cormack grade 1	899	0	482	0	324	0	93	0
Cormack grade 2	190	2	80	0	67	1	43	1
Cormack grade 3	52	10	13	4	17	2	22	4
Cormack grade 4	9	38	1	8	2	12	6	18

Table 3 Choice of anaesthetic induction mode and difficulty of intubation in the initial study

	Global population		General surgery		ENT non-cancer surgery		ENT cancer surgery	
	Intubation easy	Intubation difficult	Intubation easy	Intubation difficult	Intubation easy	Intubation difficult	Intubation easy	Intubation difficult
Topical airway anaesthesia with sedation	290	42	107	9	71	10	112	23
General anaesthesia with neuromuscular block	860	8	469	3	339	5	52	0

Table 4 Accuracy of risk factors in predicting difficult tracheal intubation (univariate analysis in 1200 patients in the initial study). DI = difficult tracheal intubation

Risk factor	True positives	True negatives	False positives	False negatives	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Association with DI (P)
Previous knowledge of DI	7	1148	2	43	14	99	78	96	< 0.00001
Pathologies associated with DI	35	1002	148	15	70	87	19	99	< 0.00001
Clinical symptoms of airway pathology	33	976	174	17	66	85	16	98	< 0.00001
Inter-incisor gap < 5 cm and mandible luxation < 0	21	1114	36	29	42	97	37	97	< 0.00001
Short thick neck	11	1065	85	39	22	93	11	96	0.001
Thyromental distance < 6.5 cm	8	1090	60	42	16	95	12	96	< 0.01
Head and neck movement < 90°	27	982	168	23	54	85	14	98	< 0.00001
Mallampati class III or IV	39	982	168	11	78	85	19	99	< 0.00001
Tooth morphology									ns

Table 5 Multivariate analysis: preoperative factors related to the occurrence of difficult intubation. DI = difficult intubation; IG = inter-incisor gap; ML = mandible luxation

Factors (in order of decreasing significance)	Stepwise significance level when added to previous factors in column	Multivariate discriminant function coefficient
Pathologies associated with DI	< 0.0001	1.63
Mallampati class 3	< 0.0001	1.93
Mallampati class 4	< 0.0001	2.52
Thyromental distance < 6.5 cm	< 0.0001	1.36
IG < 3.5 cm and ML < 0	< 0.0001	4.12
Clinical symptoms of airway pathology	< 0.0001	0.98
IG 3.5–5 cm and ML = 0	0.0009	1.09
Previous knowledge of DI	0.0084	3.28
Head and neck movement about 90°	0.0087	0.65
Head and neck movement < 90°	0.0149	1.46
Mallampati class 2	0.0255	0.66

tracheal intubation among the 12 factors studied (table 5). The multivariate discriminant function coefficient of these factors, which represents the relative predictive value of each variable, was used as "points", their sum giving the exact score. For clinical purposes, we simplified this score by arbitrarily multiplying each of the points by 3.15 and then rounding to the nearest whole number to derive a simplified point value for the factor and a simplified score. The risk factors and corresponding "points" of these two scores are presented in table 6. The optimal predictive level of the scores were determined using receiver operating characteristic curve (ROC) analysis (fig. 1). This method consists of constructing a graphic representation of each possible score level where the *Y* coordinates are the sensitivities and the *X* coordinates are the false positive percentages (= 1 − specificity). The optimal predictive level is that which is nearest to the ideal point (sensitivity = 100%, false positive = 0%). Our ideal point was 3.55 for the exact score and 11 for the simplified score (fig. 1). ROC analysis of the two scores provided a high and comparable discriminant power for predicting difficult tracheal intubation as the area under the curve was 0.958 for the exact score and 0.956 for the simplified score. Therefore, simplification of the exact score into the simplified score did not significantly decrease performance. Statistical performances of the simplified score for predicting difficult tracheal intubation in the different surgical groups, with the optimal level of 11, are presented in table 7.

SIMPLIFIED SCORE VALIDATION STUDY

Among the 1090 patients included in the validation study, 717 were undergoing general surgery, 290 for non-cancer ENT surgery and 83 for ENT cancer surgery (table 1). In the overall population, 41 patients (3.8%) had a trachea which was difficult to intubate: 18 (2.5%) undergoing general surgery, 10 (3.4%) ENT non-cancer surgery and 13 (15.7%) ENT cancer surgery. No intubation failed. Statistical performances of the score for predicting difficult tracheal intubation in the different surgical groups are presented on table 7.

Discussion

Ideally, any preoperative assessment of difficult tracheal intubation should have high sensitivity and specificity and result in minimal false positive and false negative values. The advantage of our clinical multivariate risk index is the association of high specificity with improved sensitivity in comparison with previous multivariate studies. False negative prediction is therefore minimized. In addition, the same risk index can be used for both general and ENT surgical populations.

The consequences of a false negative result may be deleterious and even life-threatening. Our predictive risk index results in minimal detection failure of difficult tracheal intubation whatever the studied population. We believe this is our most important finding. Our results are comparable with those described previously by El-Ganzouri and colleagues[18] regarding preoperative assessment of the difficult airway. Indeed, multivariable composite risk index performs better than single independent criteria. Previous work based on multivariate analyses, mainly emphasized the reduction in false positive prediction compared with a single criterion.[14–18] Although this may result in less time expended or in fewer unnecessary manoeuvres, our belief is that decreasing false negative prediction is the main goal of any prediction.

Comparing predictive values obtained from different studies based on multivariate analyses requires a brief review of the limitations of predictive risk indices and diagnostic tests. This point has been summarized previously by Dupuis, Nathan and Wynands[34]

Table 6 Risk factors retained by the multivariate analysis for predicting difficult tracheal intubation, and the corresponding points of the exact and simplified score "Points" of the exact score are given by the values of multivariate discriminant function coefficient of every factor. The "points" of the simplified score were obtained by multiplying the "points" of the exact score by 3.15 and then rounding the results to the nearest whole number

Risk factor	"Points" of the exact score	"Points" of the simplified score
Previous knowledge of difficult intubation		
No	0	0
Yes	3.28	10
Pathologies associated with difficult intubation		
No	0	0
Yes	1.63	5
Clinical symptoms of airway pathology		
No	0	0
Yes	0.98	3
Inter-incisor gap (IG) and mandible luxation (ML)		
IG ≥ 5 cm or ML > 0	0	0
3.5 < IG < 5 and ML = 0	1.09	3
IG < 3.5 cm and ML < 0	4.12	13
Thyromental distance		
≥ 6.5 cm	0	0
< 6.5 cm	1.36	4
Maximum range of head and neck movement		
Above 100°	0	0
About 90° (90° ± 10°)	0.65	2
Below 80°	1.46	5
Mallampati's modified test		
Class 1	0	0
Class 2	0.66	2
Class 3	1.93	6
Class 4	2.52	8
Total possible	15.35	48

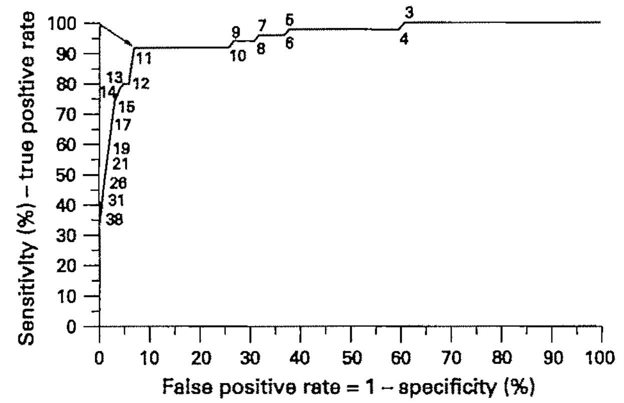

Figure 1 Receiver operating characteristic curve for the simplified score to predict difficult tracheal intubation in the global population. The numbers on the curve represent the different levels of the risk index. The sensitivity of the risk index is highest at low score values, whereas specificity is low. Highest score values give very good specificity at the expense of a reduced sensitivity. The cut-off value of 11 gives the best compromise between sensitivity and specificity.

for cardiac risk indices. A low prevalence of the "disease" (herein difficult intubation) in the test population causes the positive predictive value to decrease and the negative predictive value to increase. In our series, the overall incidence of difficult intubation was increased (3.8%) compared with previous studies[16–18] (see table 8). It might thus have favoured low negative predictive value and high positive predictive value. Nevertheless, our risk index allows the highest negative predictive value, as shown in table 8. This indicates that the risk index adequately eliminates patients without difficulties in tracheal intubation at a score level of 11, and suggests that it may be applicable to other institutions, even with a high incidence of difficult intubation. However, our risk index performs poorly for positive predictive values (30–52%). This implies that difficult intubation is falsely predicted in approximately two of three patients, or one of two patients. This is a common limitation of any risk index, as values of 9–21% have been described previously.[16–18] In our studies, as in others (table 8), the incidence of difficult intubation seems to be a major determinant of positive prediction. Nevertheless, we believe that decreasing false negative prediction is far more important than diagnosing difficult intubation in unaffected patients.

Another characteristic of the ideal predictive method is both high sensitivity and specificity. A general problem encountered with predictive risk indexes is the fact that high derived index values result in high positive predictive values, obtained with reduced sensitivity and an increased incidence of false negative predictions when considering minimal index score values. In constrast, low index score values are associated with high sensitivity and reduced false negatives, but specificity is low and false positives are increased.[34] This relationship between sensitivity and specificity is demonstrated by the ROC representation. When considering our simplified risk index at the level of 11, both sensitivity (90–94% in the various surgical populations) and specificity (66–96%) are high, especially in general surgery and ENT non-cancer surgery (see table 7). These results show improvement compared with previous studies. Sensitivity and specificity were 75%

Table 7 Predictive values of the simplified score when it is equal to or higher than 11 (best predicting cut-off) in the different surgical groups: initial and validation study (95% confidence intervals in parentheses). DI = difficult tracheal intubation

	Global population		General surgery		ENT non-cancer surgery		ENT cancer surgery	
	Initial study	Validation study	Initial study	Validation study	Initial study	Validation study	Initial study	Validation study
Incidence of DI (%)	4.2	3.8	2.0	2.5	3.5	3.4	12.3	15.7
Sensitivity (%)	92 (80.8–97.8)	93 (80.1–98.5)	92	94	87	90	96	92
Specificity (%)	93 (91.7–94.6)	93 (91.4–94.5)	98	96	95	93	71	66
Positive predictive value (%)	37 (28.4–45.3)	34 (25.2–42.7)	52	37	38	30	31	33
Negative predictive value (%)	99 (99.0–99.9)	99 (99.1–99.9)	99	99	99	99	99	98
Misclassification rate (%)	7	7	2	4	5	8	26	30

Table 8 Assessment of difficult intubation in predictive clinical multivariate studies. *Only 10% of the population had a pregnancy of more than 6 months. The different predictive values and incidences of false negatives were estimated after calculations based on the data given by the different studies

Score	Definition of difficult intubation	Population studied	*n*	Incidence (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	False negative	Misclassification rate (%)
Wilson and colleagues[17]	Cormack 3 and 4	General surgery?	778	1.5	75	88	9	99	0.4%	12
Pottecher and colleagues[16]	Cormack 3 and 4	Gynaecological and obstetric*	663	5.8	70	84	21	98	1.8%	17
El-Ganzouri and colleages[18]	Cormack class 4	General surgery?	10507	1	65	94	10	99	0.3%	7
Our simplified score	Unusual techniques	General surgery	717	2.5	94	96	37	99	0.2%	4
Our simplified score	Unusual techniques	Global population	1090	3.8	93	93	34	99	0.3%	7

and 88% for Wilson and colleagues,[17] 70% and 84% for Pottecher and colleagues[16] and 65% and 94% for El-Ganzouri and colleagues.[18] In addition, with the exception of El-Ganzouri and colleagues, these studies did not take into account the inverse relationship between sensitivity and specificity. Conversely, in the first part of our study we found that the value of 11 produced the best compromise between sensitivity and specificity, that is this is the point where the test assigned the fewest patients to the wrong category. The second part of the study confirmed the cut-off value of 11 and the misclassification rate of 7%, regardless of the number of investigators. This indicates that the reliability of the simplified risk index is investigator-independent. Finally, the main advantage of the risk index is a high sensitivity without a reduction in specificity when applied to a general surgical population. When applied to cancer ENT surgery, both sensitivity and specificity are comparable with values obtained in previous studies. The risk index can therefore be used for prediction in both general and ENT surgery.

The choice of anaesthetic technique (spontaneous or IPPV) was dependent on the anaesthetist and this may have introduced a potential bias into the study. In fact, the two modes may have potentially led to overestimation of the difficulties in tracheal intubation. During spontaneous ventilation, the patient may constrict airway muscles, reducing the laryngoscopic view, thus overestimating intubation difficulty. We tried to minimize this problem by using a meticulous and effective topical anaesthetic. In addition, when a second anaesthetist was called to intubate, he had the opportunity to deepen anaesthesia if warranted. In fact, it is not clear that the general anaesthesia mode allows a better glottic view, because with neuromuscular block the larynx is moved forwards and downwards,[35] decreasing the alignment between the pharyngeal and laryngeal axis, and thus the laryngoscopic view. In our first study, the mode of induction chosen seemed inappropriate in 298 patients (24.8%) (table 3). In 290 of 332 (87%) patients, the choice of sedation with topical anaesthesia was inappropriate, suggesting overestimation of difficult intubation. This shows that the choice of sedation and topical anaesthesia did not preclude misdiagnosis of difficult intubation in almost 87% of patients. Finally, we believe that in studying prediction of difficult intubation in different surgical populations, different modes of induction need to be included, even if a single standard method is ideal. Of previous studies, only that of Rocke and colleagues[20] used a single standard technique (thiopental followed by succinylcholine) when a difficult intubation was anticipated, as the population was limited to Caesarean section.

Another methodological question is still at issue: how to define a difficult intubation and why did we not use the Cormack and Lehane classification?[22] The reason was mainly because this classification relates only to the view gained at laryngoscopy. Despite grades 3 and 4 representing the most frequent difficulties in tracheal intubation, other causes may be involved, especially during cervical, thoracic or ENT surgery. In our first series, difficulty in glottic view was the main cause of difficulty in tracheal intubation (table 2). However, in two ENT patients, insertion of the tracheal tube was impeded by limited mouth opening, despite a good glottic view. We found the same problem in three other patients: one undergoing general surgery and two ENT surgery. In addition, numerous patients with Cormack and Lehane grade 3 and some grade 4 underwent successful intubation with usual blades and simple manoeuvres, such as external cricoid pressure or upward pressure on the epiglottis with the tip of the blade. These situations were not classified as difficult (table 2) according to our definition. With our definition for difficult intubation, our risk index aimed at predicting in which patients special laryngoscopes or techniques, not usually present in each operating room, may be required.

Our clinical predictive index has some limitations. We studied only a small number of patients with cervical spine pathology, and neither spondylosis or rheumatoid arthritis were included. Patients with occipito–atlanto–axial disease are also a high risk group,[7] not present in our studies. Thus it is possible that additional radiological evaluation may usefully complete the clinical prediction in this particular group. Another limitation is the item "previous knowledge of difficult intubation". To elucidate this during consultation is dependent on previous surgery, previous general anaesthesia with or without tracheal intubation and awareness of the patient about previously encountered difficult intubation. Omission of this information in the nine patients with this item in the initial series (table 4) would have failed to predict difficult intubation in two of seven patients with confirmed difficult intubation.

With these limitations in mind, the clinical predictive index can be applied to both general surgical and ENT populations with a general accuracy (misclassification rate 7% and errors in negative predictive value 1–2%). Its clinical use is easy, as one uses only seven risk factors and the "points" listed in table 6. Difficult intubation can be predicted if the score exceeds 11. When a score less than 11 is found, a difficult intubation can be excluded, with a risk of false prediction of 1–2%.

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British Journal of Anaesthesia 1998; 80: 147–151

Pre-emptive effect of multimodal analgesia in thoracic surgery

E. DOYLE AND G. M. R. BOWLER

Summary

Thirty subjects undergoing posterolateral thoracotomy were allocated randomly to receive one of two analgesic regimens: group Pre received i.v. morphine, i.m. diclofenac and intercostal nerve blocks from T2 to T11, 20 min before operation and placebo injections after operation. Group Post received placebo injections before operation, and i.v. morphine, i.m. diclofenac and intercostal nerve blocks from T2 to T11 at the end of surgery, before discontinuation of anaesthesia. Visual analogue pain scores, extent and duration of intercostal nerve block, analgesic consumption and complications were assessed during the postoperative period by a single blinded observer. Subjects were followed-up for a minimum of 12 months to determine the incidence of post-thoracotomy pain syndrome. During the first 48 h after operation there were lower pain scores in group Pre when taking a vital capacity breath but there were no significant differences between the groups in any other measure. The effects of pre-emptive analgesia given before surgery appeared to be relatively modest in terms of analgesia, analgesic consumption and long-term outcome and were of limited clinical significance. (*Br. J. Anaesth.* 1998; **80**: 147–151)

Keywords: analgesia, pre-emptive; surgery, thoracic; complications, post-thoracotomy syndrome

Evidence from basic research in mechanisms of pain suggests that administration of analgesic drugs may be more effective if given before, rather than after, a nociceptive stimulus.[1–3] Some clinical work supports this concept when using local anaesthetic techniques,[4 5] systemic opioids,[6–8] extradural opioids,[9] ketamine[7] and combined or balanced analgesic regimens.[10] Other studies have found little difference in the degree of postoperative pain or requirements for analgesics between groups where analgesics are administered after rather than before the start of surgery using opioids,[11 12] local anaesthetics,[13–17] non-steroidal anti-inflammatory drugs (NSAID)[18 19] or combined techniques.[20–22]

The proposed mechanism of this pre-emptive effect is that administration of analgesia before a nociceptive stimulus reduces the degree of sensitization produced in the nervous system by the stimulus and facilitates subsequent treatment. Noxious stimulation generates reflex hyperexcitability in the dorsal horn of the spinal cord.[23] This central sensitization prolongs and increases sensitivity to noxious stimuli over an expanded receptive field (hyperalgesia), results in pain from normally innocuous stimuli (allodynia) and in spontaneous pain. Repetitive noxious stimuli evoke a progressively escalating response in the spinal cord which further magnifies the pain.[24] An extension of this concept is that effective analgesia administered before a nociceptive stimulus may also reduce the risk of a postoperative chronic pain syndrome.[25]

It is important to discriminate between the effects of pre-emptive analgesia where the same intervention is compared when given before or after the nociceptive stimulus, and preoperative analgesia where analgesia is given before surgery and compared with no intervention or with placebo. Administration of analgesia before surgery compared with no intervention or with placebo is known to provide superior analgesia and to reduce pain compared with placebo.[4 24] The appropriate design of a study to detect the pre-emptive effects of an analgesic, if any, has been described[26] and this study was performed in accordance with that design.

We designed this study to eliminate these factors by studying a major procedure associated with consistently high scores in measures of postoperative pain,[27] adhering to the appropriate design for a study of pre-emptive analgesia and using a combined opioid, NSAID and local anaesthetic–analgesic regimen. We also studied the effect on postoperative chronic pain syndrome associated with thoracotomy to determine if the practice of pre-emptive analgesia had any effect on the incidence of this problem.

Patients and methods

The study was approved by the local Ethics Committee and informed written consent was obtained from each subject. We studied 30 subjects undergoing unilateral posterolateral thoracotomy for lobectomy or pneumonectomy. Exclusion criteria included any history of a chronic pain condition, current use of analgesic medications or contraindications to the use of non-steroidal anti-inflammatory drugs. Before operation, all subjects were instructed in the use of patient-controlled analgesia (PCA) and the use of a 100-mm visual analogue scale for reporting of pain, and introduced to the use of blunt tipped 27-gauge dental injection needles for determination of the extent of local anaesthetic block.

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Table 1 Patient data and operative procedures (mean (SD or range) or number)

	Group Pre	Group Post
Sex (M:F)	12:3	11:4
Age (yr)	61.6 (34–79)	59.8 (30–72)
Weight (kg)	73.7 (9.8)	72.8 (11.3)
Procedure		
(Lobectomy:pneumonectomy: thoracotomy without lung resection)	8:6:1	9:3:3
Side (R:L)	6:9	8:7
Duration of surgery (min)	119 (56)	95 (34)
Duration of postoperative chest drainage (h) (median (range))	48 (17–144)	42 (12–164)

Subjects were premedicated with temazepam 20 mg orally, 1–2 h before operation. Anaesthesia was induced after preoxygenation with propofol 2–3 mg kg^{-1} and atracurium 0.6 mg kg^{-1}. After tracheal intubation with an appropriate double-lumen tube and verification of its position, the lungs were ventilated with 1–5% enflurane and nitrous oxide in oxygen, and an infusion of atracurium 0.5 mg kg^{-1} h^{-1} was commenced. The concentration of enflurane during surgery was varied as required to maintain heart rate and arterial pressure within 20% of pre-induction values. All surgical procedures were performed by the same surgeon in the morning of the same day of the week.

Subjects were allocated randomly using computerized randomization to one of two groups. In group Pre, subjects received morphine 10 mg i.v., diclofenac 75 mg i.m. and intercostal nerve blocks in spaces 2–11 with a total 40 ml of 0.5% bupivacaine with epinephrine 1/200 000 and 8.4% sodium bicarbonate 1 ml which has been shown to increase the duration of intercostal nerve block produced by bupivacaine and epinephrine.[28] In group Post, subjects received dummy i.v. and i.m. injections and a series of dummy intercostal nerve blocks. No other analgesics were administered during surgery. The start of surgery was then delayed for at least 20 min after administration of analgesic or dummy injections to ensure that any analgesic intervention was effective before nociceptive stimulus.

At the end of surgery, subjects in group Pre received dummy i.v. and i.m. injections and a series of dummy intercostal nerve blocks. Subjects in group Post received morphine 10 mg i.v., diclofenac 75 mg i.m. and intercostal nerve blocks with a total of 40 ml of 0.5% bupivacaine with epinephrine 1/200 000 and 8.4% sodium bicarbonate 1 ml. Anaesthesia was maintained for another 20 min before antagonism of neuromuscular block and discontinuation of anaesthesia. All analgesic procedures were performed by a single investigator.

Postoperative management of subjects in both groups was identical. When patients were able to co-operate they gave a visual analogue score for pain and the extent of intercostal nerve block was assessed. If there was an inadequate intercostal nerve block the blocks were repeated. In the event of pain outside the distribution of the intercostal nerves, subjects received increments of morphine 2 mg until they were pain free. Subsequently, subjects administered PCA using morphine 60 mg in 0.9% saline 60 ml (1 mg ml^{-1}) containing metoclopramide 60 mg. The bolus dose was 1 mg, background infusion 0.5 mg h^{-1} and lockout interval 6 min. Diclofenac 50 mg orally was administered every 8 h. Additional boluses of morphine 5 mg were prescribed and administered by nursing staff if the visual analogue score was persistently greater than 40 mm. Intercostal nerve blocks were repeated by the same investigator as previously if a subject was in significant pain (visual analogue score >40 mm), was unable to cough and clear secretions and had no demonstrable remaining intercostal nerve block. Physiotherapy and nursing care were given by the same people to patients in both groups.

Assessments of pain were performed in the recovery area and at 6, 12, 18, 24, 30, 42 and 48 h after operation. On these occasions subjects gave a visual analogue score from 0–100 mm for pain before and after taking a vital capacity breath and the extent of the intercostal nerve block was assessed using a 27-gauge blunt tipped dental injection needle. Ventilatory frequency and arterial oxygen saturation were also noted at these times. Other assessments made were time to first oral intake and duration of chest drainage. All assessments were performed by a single observer who was unaware of the intraoperative analgesic management of the subjects.

After 48 h, PCA was discontinued and analgesia provided with dihydrocodeine 60 mg orally every 4 h as required, morphine 10 mg i.m. every 3 h as required and diclofenac 50 mg orally every 8 h as required. Analgesic consumption during the following week and duration of hospital stay were also noted.

At 6 and 12 months after operation, patients' notes were examined to determine if they were still alive. If so a telephone call was made and subjects were asked about the occurrence of symptoms of post-thoracotomy pain or post-thoracotomy syndrome using the definition of the International Association for the Study of Pain[29] of pain that recurs or persists along a thoracotomy scar at least 2 months after surgery. Specific questions were asked about a burning or aching quality to the discomfort, pain caused or worsened by routine stimuli and delayed or exaggerated responses to routine stimuli. Current analgesic consumption for pain at the site of the thoracotomy was elicited. All of these calls were made by the same blinded observer.

We calculated that this study had a power of 80% to detect differences between groups which would be significant at the 5% level. This calculation was similar to that used in several other studies investigating the presence or absence of pre-emptive analgesia in clinically relevant circumstances.[9, 16, 20] Statistical analysis was performed using the Student's *t* test for normally distributed data and the Mann–Whitney *U* test for skewed data.

Results

The two groups were similar in patient data and operative procedures (table 1).

In all subjects there was an intercostal block from T2 to T11 on the side of surgery in the recovery area. One subject in group Pre and two in group Post required i.v. morphine in the recovery area.

There was no difference between groups in postoperative consumption of morphine by patient-

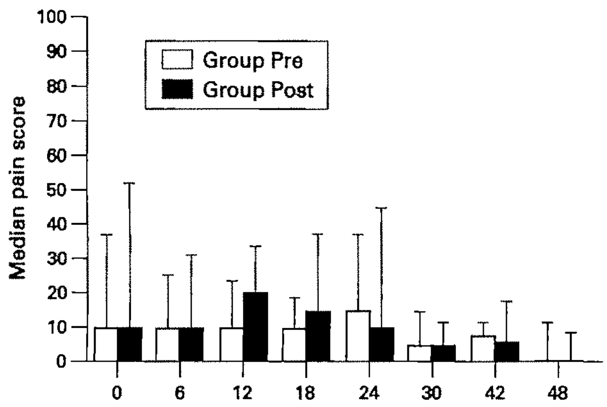

Figure 1 Median visual analogue pain scores in groups Pre and Post at rest during the postoperative period.

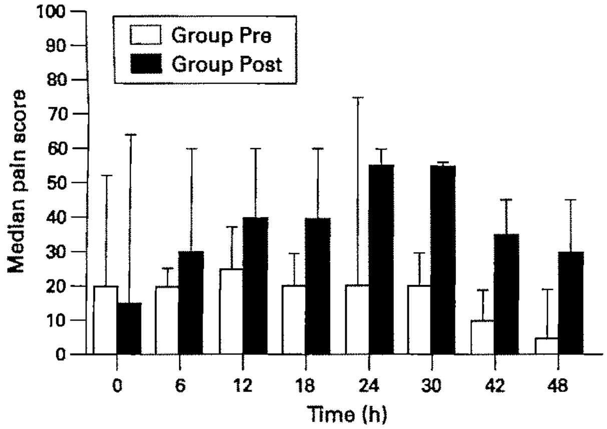

Figure 2 Median visual analogue pain scores in groups Pre and Post during a vital capacity breath during the postoperative period. $P < 0.05$.

Table 2 Requirements for analgesia during postoperative days 2–7 in group Pre and group Post (median (range) number of doses)

	Group Pre	Group Post
Diclofenac	12 (1–19)	12 (6–16)
Dihydrocodeine	7 (1–16)	9 (3–17)
Morphine	0 (0–3)	1 (0–4)

controlled analgesia. Subjects in group Pre consumed a median of 92 (range 50–136) mg and those in group Post 82 (32–128) mg during the first 48 h after operation. Total morphine consumption comprising morphine by patient-controlled analgesia and additional boluses of 5 mg administered by nursing staff was 95 (50–156) mg in group Pre and 82 (32–172) mg in group Post.

There was no difference in visual analogue scores between patients at rest in group Pre and group Post at any of the assessments during the postoperative period (fig. 1).

In group Post, VAS scores during a vital capacity breath were significantly higher ($P < 0.05$) than those in group Pre at all assessments other than in the recovery area and at 6 h after operation (fig. 2). There was a consistent increase in VAS pain scores during a vital capacity breath over the first 36 h after operation in group Post but not in group Pre.

There was no difference between groups in duration of intercostal nerve block. Median duration of detectable block was 27 (range 8–42) h in group Pre and 24 (18–48) h in group Post. Two subjects in group Pre and three in group Post received repeat intercostal nerve injections on the day after surgery.

During the period from 48 h to 7 days after operation, there was no difference between groups in consumption of diclofenac, dihydrocodeine or morphine administered for pain (table 2).

There was no difference between groups in the time taken to first oral fluid intake, with a median of 9 (range 3–25) h in group Pre and 15 (4–22) h in group Post. There was no difference in the time of discharge from hospital (6 (5–14) days in group Pre and 6 (4–8) days in group Post). Two subjects in group Post were excluded from this analysis as they were transferred to other hospitals for management of a bleeding duodenal ulcer and for nursing care, respectively.

At telephone follow-up, two subjects in group Pre and none in group Post described symptoms of post-thoracotomy neuralgia. One subject in group Post was excluded from this analysis because he underwent subsequent lung transplantation.

Discussion

We have found an effect of pre-emptive analgesia on postoperative visual analogue pain scores during the 48 h after operation which was limited to a reduction in VAS pain scores during a vital capacity breath. There were no differences between groups in analgesic consumption, complications or long-term outcome, including the incidence of post-thoracotomy pain. This is despite the use of a model of severe postoperative pain, a design which fulfilled the requirements to detect any pre-emptive analgesic effect and a tightly controlled study design.

Thoracotomy is one of the most painful surgical procedures known, with multiple sources of nociception, including the surgical incision, disruption of ribs and intercostal nerves, pleural inflammation, pulmonary parenchymal damage and the presence of postoperative intercostal drains. The fact that all subjects received both preoperative and postoperative analgesics or placebo fulfils the requirement to detect a pre-emptive analgesic effect. All procedures involved posterolateral thoracotomy performed by the same surgeon while all analgesic interventions were performed by the same consultant anaesthetist and a single blinded observer performed all postoperative assessments to eliminate variability between observers. The similar timing of surgery in both groups implies that events which may have been influenced by ward routines, such as chest drain removal and hospital discharge, should have been influenced in the same way to a similar extent in both groups. The prolonged follow-up of these subjects is unique in studies of pre-emptive analgesia and was designed to detect any difference between groups in the incidence of post-thoracotomy neuralgia. Previous studies have suggested that the incidence and severity of chronic pain after surgery may be modified by the perioperative analgesic regimen[25] but we were unable to find evidence to support this suggestion.

Various reasons why the work performed in animals is not consistently replicated in clinical practice have been suggested. In some of the studies which showed no effect, an appropriate pre-emptive study design was not used with analgesic premedication being administered[15] or analgesic drugs being given before the surgical incision.[13, 17–19, 22] The fact that subjects in this study did not undergo surgery until at least 20 min after the first set of injections and were kept anaesthetized for 20 min after the second set implies that subjects in group Pre had effective clinical analgesia at the start of surgery and subjects in group Post did not emerge from anaesthesia until their analgesic interventions were effective, although it may be that the NSAID component of the analgesic treatments requires more than 20 min to become fully effective.

Several studies have used as models relatively minor surgical procedures such as wisdom teeth extraction,[16] which produce low intensity noxious stimuli that may not generate enough difference between pre-emptive and control groups to demonstrate a clinical effect. In addition, relatively minor surgery may not trigger the altered central processing of sensory inputs which causes subsequent hyperalgesia and allodynia.[30] Conversely, the nociceptive stimulation which is produced during surgery with mixed cutaneous, visceral and muscular components, in addition to emotional or psychological factors, may be more difficult to prevent than that arising from the limited physical and chemical insults used in experimental animals. Clinical postoperative pain is a different entity from nociception inflicted during animal studies and it is not surprising that it is more difficult to demonstrate a genuine pre-emptive effect in this situation compared with animal models. Infusion analgesic regimens which are not titrated to patient request and which produce pain scores of zero may obscure any pre-emptive effect unlike on-demand analgesic regimens where analgesic consumption is determined by the patient and acts as an indicator of the degree of pain or nociception present.

Our analgesic management clearly failed to provide complete ablation of nociceptive stimuli during anaesthesia and surgery, as demonstrated by the requirement for analgesia in the recovery area in several patients, particularly for pain in the shoulder region out with the area of intercostal nerve block. These subjects were not excluded from the analysis because our intention was to compare a clinically relevant pre-emptive analgesic regimen with a clinically relevant non-pre-emptive analgesic regimen accepting that occasionally patients may not have complete analgesia on recovery from anaesthesia. This was despite intercostal nerve blocks, attempting to limit the production of inflammatory mediators with a systemic NSAID and suppressing the central perception of nociception with systemic opioid. Sympathetic and parasympathetic afferents would not have been blocked by our analgesic regimen and neither would the phrenic nerve, which is sensory to the pericardium, mediastinal and diaphragmatic pleura. This fact may also have served to obscure any pre-emptive analgesic effect in group Pre. It would only have been possible to ablate nociceptive stimuli completely in this group by using analgesic regimens which are not clinically relevant, such as very high extradural block or high-dose opioid which would both have presented problems of their own and necessitated postoperative ventilation. Alternatively, the use of interpleural analgesia may have produced a more widespread afferent block from the operated side.

The increase in VAS pain scores during a vital capacity breath in group Post but not in group Pre suggests that sensitization occurred in group Post either peripherally through inflammation, spinally or centrally. The absence of this increase in group Pre may be a manifestation of a pre-emptive analgesic effect.

In summary, this study adds to the growing body of evidence that the effects of pre-emptive analgesia given before surgery are relatively modest in terms of analgesia, analgesic consumption and long-term outcome, and are of limited clinical significance.

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Combining propofol with morphine in patient-controlled analgesia to prevent postoperative nausea and vomiting

S. E. Bree, M. J. West, P. A. Taylor and I. G. Kestin

Summary

We have studied the antiemetic effects of propofol when mixed with morphine in a patient-controlled analgesia (PCA) pump after major gynaecological surgery. In a double-blind, randomized, controlled study, 50 women, ASA I or II, received a standardized anaesthetic comprising thiopental, morphine, atracurium, nitrous oxide and oxygen with enflurane, and received postoperative PCA with morphine mixed with either 1% propofol or Ivelip. The PCA bolus was morphine 1 mg with propofol 5 mg or Ivelip 0.5 ml, with a lockout time of 5 min. Postoperative nausea and vomiting (PONV) were assessed by the nursing staff using a four-point ordinal scale and by the patient using a visual analogue scale for 48 h after surgery. The two groups were similar in the potential factors influencing the incidence of PONV. There were no significant differences between the two groups in any of the study measurements of PONV. There were no side effects after propofol. Propofol, when mixed with morphine in this dose combination for PCA, did not decrease the incidence of nausea and vomiting in women undergoing major gynaecological surgery. (*Br. J. Anaesth.* 1998; **80**: 152–154)

Keywords: anaesthetics i.v., propofol; analgesics opioid, morphine; vomiting, nausea; vomiting, postoperative; analgesia, patient-controlled

Postoperative nausea and vomiting (PONV) is one of the more common and distressing causes of morbidity after major surgery. There is a decreased incidence of PONV after propofol.[1–4] Whether propofol has direct antiemetic properties or is merely less emetogenic than other anaesthetic drugs is not known. There has been interest in using subhypnotic doses of propofol both to treat and prevent nausea and vomiting after cancer chemotherapy and surgery.[5–8] Small doses of propofol given in recovery were successful in treating PONV,[7] but the results with postoperative infusion for 24–48 h after surgery were conflicting.[8–11] We have studied the effects of simultaneous administration of propofol and morphine patient-controlled analgesia (PCA) on the incidence of PONV.

Patients and methods

After obtaining approval from the local Ethics Committee, we studied ASA I or II women, aged 30–75 yr, undergoing elective hysterectomy (either abdominal or vaginal). We excluded women weighing more than 100 kg, those who were unable to use patient-controlled analgesia (PCA) and any patient who suffered from epilepsy, ear disease, liver disease, hyperlipidaemia or were receiving drugs with antiemetic properties.

After obtaining written informed consent, all patients were premedicated with temazepam 20–30 mg, 1 h before surgery. Anaesthesia was induced with thiopental, atracurium and morphine 0.2 mg kg^{-1}, and maintained with enflurane (end-tidal 0.5–2%) and 60% nitrous oxide in oxygen. At the end of surgery residual neuromuscular block was antagonized with neostigmine 2.5 mg and glycopyrrolate 0.5 mg. After extubation of the trachea all patients were transferred to the recovery area where they received a PCA (Graseby 3300) consisting of morphine 100 mg mixed in 50 ml of either 1% propofol or 10% Ivelip (10% soya oil, 2.5% glycerol, Clintec).

Derriford Hospital Pharmacy prepared all the study solutions under aseptic conditions and randomized the patients. The stability of morphine, propofol and Ivelip mixtures have been verified previously by HPLC (Dr P. Adams, principal pharmacist, South West Pharmaceutical Quality Control Laboratory, Torbay Hospital, Torquay, personal communication). The patient, anaesthetist, investigators and all nurses were unaware of the contents of the syringe. Another two syringes, each containing 1 ml of either propofol or 10% Ivelip, were supplied by the pharmacy with the appropriate PCA syringe. The first 1-ml bolus was given i.v. by the recovery nurse if the patient complained of nausea or was vomiting. The second syringe was given 5 min later, followed by rescue antiemetic (prochlorperazine 12.5 mg i.m. every 6 h) after another 5 min, as required. The PCA pump was programmed to give morphine 1 mg with either propofol 5 mg or Ivelip 0.5 ml in each successful demand, with a lockout of 5 min. The maximum possible dose of propofol in 1 h was 60 mg. A separate i.v. cannula was used for the PCA. All patients were prescribed oxygen for 24 h and when comfortable were transferred to the ward.

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Table 1 Patient characteristics and recovery times (number (%), or mean (SD) [range])

	Propofol (n=25)	Ivelip (n=24)
Age (yr)	45 [30-75]	46 [33-67]
Weight (kg)	70 (12.6)	68 (14.2)
Body mass index	26 [17-33]	25 [18-32]
History of motion sickness	3 (12%)	1 (4%)
History of PONV	9 (36%)	5 (20%)
Duration of anaesthesia (min)	100 (23.5)	96 (20.3)
Time in recovery (min)	69 (33.5)	70 (28.8)

Table 2 Analgesia and sedation in the two groups (mean (95% confidence intervals) or median [range])

	Time	Propofol	Ivelip
Morphine (mg)	0-24 h	47 (36-58)	40 (30-50)
	24-48 h	12 (4-20)	5 (2-9)
Pain VAS	0-24 h	3.3 [0-8.0]	3.4 [0-9.2]
	24-48 h	2.2 [0-8.5]	1.0 [0-8.3]
Sedation	0-24 h	2.0 [1.3-3.8]	2.0 [1.3-4.3]
	24-48 h	1.3 [1.0-2.0]	1.0 [1.0-3.0]
Propofol (mg h^{-1})	0-24 h	9.8 (7.5-12.1)	
	24-48 h	2.6 (0.9-4.2)	

Table 3 Incidence of PONV and use of antimetics in the two groups (number (%) or median [range])

	Propofol (n=25)	Ivelip (n=24)
Nausea ± vomiting		
0-24 h	17 (68%)	16 (67%)
24-48 h	3 (12%)	2 (8%)
Mean nausea score		
0-24 h	1.3 [1-2.3]	1.2 [1-1.8]
24-48 h	1 [1-2]	1 [1-1.7]
Nausea VAS		
0-24 h	2.4 [0-10]	2.0 [0-10]
24-48 h	0 [0-9.1]	0 [0-6.4]
Single bolus given in recovery	3 (12%)	4 (16%)
Double bolus given in recovery	3 (12%)	2 (8%)
Rescue antiemetic given in recovery	0	2 (8%)
Prochlorperazine		
0-24 h	15 (60%)	16 (67%)
24-48 h	3 (12%)	2 (8%)

At 4-hourly intervals for the first 24 h, and 8-hourly intervals for the second 24 h, the ward nurses recorded PCA demands and doses, nausea scores, episodes of vomiting, antiemetics given and sedation scores.

PONV was recorded as: (1) no nausea or vomiting; (2) nausea alone; (3) nausea with vomiting on one or two occasions; and (4) nausea with vomiting more than twice. Sedation was recorded as: (1) awake; (2) dozing intermittently; (3) mostly sleeping; and (4) only awakens when aroused.

Mean nausea scores for each patient were obtained as the mean of the nursing PONV scores during each 24-h period. In addition, at 24 and 48 h, patients completed two 10-cm visual analogue scales (VAS) for pain and nausea, ranging from none to the worst possible. The amount of morphine and rescue antiemetics given by the nurses were also recorded.

The sample size was chosen to provide a 75% probability of demonstrating a reduction in the incidence of PONV from 60% to 30% when α=0.05. The data were analysed using the Student's t test, Mann–Whitney U test and Fisher's exact test, where appropriate (Instat v2.01, GraphPad; Macintosh System B-7.01), and the level of statistical significance was 5%.

Results

A total of 50 patients were entered into the study. One patient receiving Ivelip was excluded within the first 24 h because of excessive sedation; 25 patients received propofol and 24 received Ivelip. Patient characteristics, duration of anaesthesia and time spent in recovery were similar in both groups (table 1).

The amount of morphine used from the PCA, visual analogue scores for pain and sedation scores were similar in both groups at 24 and 48 h (table 2). There were no significant differences between the two groups in any of the measurements of PONV (table 3).

Discussion

Postoperative nausea and vomiting (PONV) after anaesthesia is less likely with propofol than with other anaesthetic agents, and the magnitude of the reduction depends on the method of administration, time of measurement and baseline incidence of PONV.[4] PONV is least when propofol is used for maintenance and induction of anaesthesia.[4] The action of propofol on dopamine[12-14] and 5HT$_3$ receptors[15] has been investigated, and it seems unlikely that propofol has important activity at these receptors.

There has been interest in using propofol specifically as an antiemetic drug, both as treatment and for prophylaxis.[1] Propofol 10 mg given in recovery was effective in 69% of patients with established PONV (compared with 35% responding to placebo).[7] Schulman, Rockett and Canada reported that a patient with severe refractory PONV was treated successfully with a propofol infusion for 5 days.[16] Gan and colleagues have published their preliminary results using a target-controlled infusion of propofol to treat PONV in recovery.[17] Patients with PONV were given infusions of propofol in increasing doses until treatment was successful or the study limit (a target concentration of 800 ng ml^{-1}) was reached. They found that a target concentration of 405 ng ml^{-1} reduced the verbal nausea score to less than 3 or by 50%. This blood concentration of propofol would normally be obtained with a bolus dose of 10 mg and an infusion of 1 mg kg^{-1} h^{-1}. Details of the patients, anaesthetic techniques and whether a control group were used were not given.[17]

Postoperative infusions of propofol have been tried as prophylaxis against PONV, with conflicting results.[8-11] Patients in the study by Ewalenko and colleagues[8] received an infusion of propofol started in recovery after thyroid surgery. The incidence of PONV was reduced from 65% (in the control group) to 10%,[8] but patients in two other studies did not benefit from using propofol in this way.[9 10] In these three studies,[8-10] propofol was not used for anaesthesia, although Scudieri and colleagues[10] started the subhypnotic infusion of propofol before anaesthesia and surgery. Modest success has been reported in reducing the severity of PONV after intrathecal morphine using a postoperative infusion of propofol for 24 h.[11]

Our premise when starting this study was that by coupling the dose of propofol to that of morphine and by using boluses, which have been shown to be effective, propofol with morphine in a PCA may be an effective technique for both analgesia and antiemesis. In addition, continuous infusion of propofol requires an additional i.v. cannula and syringe driver, and we found this a practical disadvantage in our previous study.[9] The maximum dose of propofol that could be obtained from the PCA pump was 60 mg in 1 h; in practice, the mean propofol dose was much less than this, and the maximum dose of propofol received during any 4-h period by a patient in this study was 180 mg. This is considerably less than would be delivered using the 1-mg kg^{-1} h^{-1} scheme of previous studies of continuous postoperative infusions of propofol.[9 10] The dose of propofol obtained by the patients from the PCA in our study may have been too low if propofol does indeed have antiemetic properties. We chose a propofol bolus dose of 5 mg, which we thought would be safe for the patients to receive on the ward. If we had used a 10-mg bolus, and morphine consumption remained the same, the mean hourly propofol dose would have been 19.6 mg in the first 24 h. This is still less than 1 mg kg^{-1} h^{-1} used previously for prophylaxis of nausea and vomiting after surgery[9 10] or cancer chemotherapy.[5 6] However, the patient who used the most propofol in any 4-h period in this study would have received a mean of 90 mg per hour if a 10-mg propofol bolus had been chosen. She weighed 68 kg, so the dose would have been more than 1 mg kg^{-1} h^{-1} during this time; this may not be safe on a general ward.

In summary, we believe that it is unlikely that propofol will have important postoperative use in treating or avoiding PONV.

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British Journal of Anaesthesia 1998; **80**: 155–158

Prophylaxis for vomiting by children after tonsillectomy: ondansetron compared with perphenazine

W. M. SPLINTER AND E. J. RHINE

Summary

We have compared the effects of ondansetron and perphenazine on vomiting after tonsillectomy in 216 healthy children, aged 2–12 yr. The study was randomized, stratified, blocked and double blind. Anaesthesia was induced with propofol i.v. or by inhalation of halothane and nitrous oxide. Ondansetron 150 μg kg^{-1} or perphenazine 70 μg kg^{-1} was administered i.v. after induction of anaesthesia in a double-blind manner. Perioperative management of emesis, pain, fluids and patient discharge were standardized. Ondansetron and perphenazine had similar effects on postoperative vomiting (44% *vs* 41%; ondansetron *vs* perphenazine P=0.77). By logistic regression analysis, the only significant predictor of postoperative vomiting was sex, that is males had a greater incidence of vomiting (49% *vs* 35%; P=0.016). In-hospital vomiting was associated with a prolongation of stay in the day-care surgical unit of 7 min per episode of vomiting (P=0.015). We conclude that ondansetron and perphenazine had similar effects on vomiting in children after tonsillectomy in a day-case setting. (*Br. J. Anaesth.* 1998; **80**: 155–158)

Keywords: anaesthesia, paediatric; surgery, otolaryngological; vomiting, antiemetics, ondansetron; vomiting, antiemetics, perphenazine

Vomiting is a common, unpleasant sequel to surgery and anaesthesia and may result in dehydration, important electrolyte disturbances, delayed discharge from hospital and unscheduled admission to hospital.[1–3] Children undergoing tonsillectomy are at particular risk of vomiting, with as many as 71–73% of children vomiting after tonsillectomy.[4] Anaesthetists are searching for cost-effective techniques that may minimize this problem.

Ondansetron and perphenazine are antiemetics that decrease vomiting after tonsillectomy in children.[4 5] For many, ondansetron has become the "gold standard" antiemetic because of its efficacy and minimal side effects compared with alternatives. Unfortunately, ondansetron is expensive. Perphenazine is a phenothiazine with moderate anticholinergic effects, weak to moderate sedative effects and potent antiemetic effects. Compared with ondansetron, perphenazine had similar antiemetic effects and fewer side effects in adults after hysterectomy.[6] We have evaluated the hypothesis that ondansetron and perphenazine have similar effects on vomiting in children after tonsillectomy.

Patients and methods

Healthy children, aged 2–12 yr, undergoing elective tonsillectomy or adenotonsillectomy were enrolled in this randomized, stratified, blocked, double-blind study after obtaining approval from our Ethics Committee. Within the balanced study design, blocks of five patients were stratified according to use of premedication and technique for induction of anaesthesia so that a similar number of patients in each study group received premedication and the two available induction techniques. The children were allocated randomly to receive ondansetron or perphenazine in a double-blind manner. Exclusion criteria included allergy to a study drug, history of sleep apnoea or ASA III or greater.

Patients were permitted to drink clear fluids for up to 3 h before anaesthesia, but did not ingest solid food on the day of surgery. Those children requiring premedication received midazolam 0.5 mg kg^{-1} (maximum dose 15 mg) orally, 20–30 min before induction of anaesthesia. General anaesthesia was induced by inhalation of nitrous oxide and halothane or propofol 2.5–3.5 mg kg^{-1} i.v. Mivacurium 0.25 mg kg^{-1} was administered if a neuromuscular blocking agent was indicated to facilitate tracheal intubation. Ondansetron 150 μg kg^{-1} (maximum dose 8 mg) or perphenazine 70 μg kg^{-1} (maximum dose 5 mg) was administered i.v. in a double-blind manner immediately after induction of anaesthesia. The dose for perphenazine was extrapolated from the adult dose of 5 mg. Anaesthesia was maintained with 0.75–2.0% halothane and 70% nitrous oxide in oxygen. Midazolam 50 μg kg^{-1} (maximum dose 3 mg) i.v. was given if the child had not received it for premedication. (Midazolam was given to all patients because it has been shown to have antiemetic effects in children undergoing tonsillectomy.[7]) All patients received codeine 1.5 mg kg^{-1} i.m. in the right thigh before commencement of surgery. Intraoperative i.v. fluid comprised lactated Ringer's solution at half the calculated deficit during the first hour, plus main-

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Table 1 Confounding variable distribution (number of patients)

Group	Premedication	Propofol induction	Inhalation induction
Ondansetron	21	55	54
Perphenazine	19	55	52

Table 3 Incidence of postoperative vomiting. PAR= post-anaesthetic recovery room, DCSU=day-case surgical unit, Day 0=day of surgery, Day 1=day after surgery

	In hospital		Out of hospital		
Group	PAR	DCSU	Day 0	Day 1	Overall
Ondansetron	2%	11%	20%	26%	44%
Perphenazine	2%	15%	22%	25%	41%

Table 4 Incidence of vomiting over 24 h by subgroup (number (%))

	Ondansetron	Perphenazine
Oral midazolam	8/21 (39)	6/19 (50)
No premedication	40/88 (45)	38/88 (43)
Propofol induction	26/55 (47)	22/55 (40)
Inhalation induction	22/54 (40)	22/52 (43)
All cases	47/109 (59)	55/130 (42)

tenance fluids, in addition to replacement of four times the estimated blood loss with crystalloids.

Management of postoperative emesis, pain and fluids was standardized. Vomiting was defined as the forceful expulsion of liquid gastric contents. Retching and nausea were not considered vomiting. Nursing staff and parents were aware of this definition of vomiting. Nursing staff recorded vomiting in the charts, which is standard practice in our hospital. Patients who vomited twice in hospital received dimenhydrinate 1 mg kg^{-1} i.v. Parents were contacted 24 h after surgery by a research assistant to ascertain the number of times their child vomited after discharge from hospital and what the parents had done in response to the vomiting. Pain in the post-anaesthesia recovery room (PAR) was treated with morphine 50 µg kg^{-1} i.v., while subsequent pain was treated with acetaminophen or codeine, or both, in the day-case surgical unit (DCSU) and at home. I.v. fluid comprised lactated Ringer's solution at twice maintenance rates in the PAR and DCSU. Patients were encouraged, but not coerced, to drink clear fluids in the DCSU before discharge. Patients were discharged following a recommended hospital policy of a minimum 4-h stay in the DCSU and after ingestion of clear fluids.

Continuous, normally distributed data, such as patient age, were compared using one-way ANOVA, and continuous, non-normally distributed data, such as length of stay in the DCSU, were compared using the Mann–Whitney *U* test. Binomial data, such as incidence of vomiting, were compared using chi-square analysis and Fisher's exact test, where appropriate. Logistic regression analysis was used to detect if factors such as study drug, age, weight, in-hospital analgesics, premedication, use of neuromuscular blocking agents, operative time, estimated intraoperative blood loss and induction technique were significant predictors of vomiting. Stepwise linear regression analysis was used to assess the effect of study group, in-hospital vomiting, age, premedication and induction technique on length of stay in the DCSU. Sample size was determined by assuming that the acceptable difference in vomiting was 20%. The alpha error was set at 0.05 (two-sided) and type II error was at 0.20. The projected sample size was 110 patients per group after consideration of potential dropouts.

Results

Over a period of 6 months, 220 patients were enrolled. Four patients were subsequently excluded because of major study violations. The groups were similar after stratification and blocking of patients (table 1) and they had similar characteristics (table 2). Mivacurium was administered to 86 patients in the ondansetron group and to 83 patients in the perphenazine group. No patient required antagonism of neuromuscular block. Duration of stay in the PAR was similar in the two groups (mean 46 min *vs* 47 min for the ondansetron and perphenazine groups, respectively) but in the DCSU, ondansetron-treated patients had a briefer stay (median 235 (range 165–305) min *vs* 240 (175–430) min; ondansetron *vs* perphenazine, P=0.007). Analgesic use in hospital was similar. In the ondansetron group, four patients received morphine in the PAR and 108 patients received codeine in the DCSU, while in the perphenazine group, seven patients received morphine in the PAR and 107 patients received codeine in the DCSU.

Episodes of vomiting per patient ranged from 0 to 11. Fifteen patients in the ondansetron group vomited three or more times, while 19 patients in the perphenazine group vomited three or more times. The study groups had a similar incidence of vomiting (table 3). By logistic regression analysis, the sex of the child was a significant (P=0.013) predictor of postoperative vomiting, with 49% of males and 35% of females vomiting. Other potential predictors (study group, age, weight, induction technique, premedication, duration of anaesthesia, estimated intraoperative blood loss, use of neuromuscular blocking agents and use of in-hospital postoperative opioids) of vomiting were not significant (table 4). Patients who vomited twice while in hospital received a rescue antiemetic (dimenhydrinate) which was given to four patients in the ondansetron group and to seven patients in the perphenazine group.

Six patients were admitted or readmitted to hospital after discharge, five of whom were in the ondansetron group. Four of these patients were admitted for surgical reasons: bleeding (n=3) or

Table 2 Patient and surgical data (mean (SD), median (range) or number)

Group	n	Age (yr) (mean (range))	Weight (kg)	Length of anaesthesia (min)	Blood loss (ml)	Sex (M/F)
Ondansetron	109	7.1 (2–12.5)	29 (15)	31 (11)	15 (0–225)	49/60
Perphenazine	107	6.8 (2–12.8)	26 (12)	32 (13)	15 (0–220)	49/58

refusing to drink (n=1). One patient in the ondansetron group required in-hospital management of emesis and one patient was admitted for management of exacerbation of asthma.

Duration of stay in the DCSU was affected significantly by two factors: (1) in-hospital vomiting (P=0.01) and (2) study drug (P=0.02). Each episode of in-hospital vomiting prolonged DCSU stay by 7 min. Patients in the perphenazine group stayed in the DCSU for an average of 7 min longer than patients in the ondansetron group. No adverse events, such as extrapyramidal symptoms or allergic reactions, possibly attributable to ondansetron or perphenazine, were observed or reported by the nursing staff or parents.

Discussion

Ondansetron and perphenazine were observed to have similar effects on the incidence of vomiting in children after tonsillectomy. These similarities in the antiemetic effect were noted in hospital and after discharge. The incidence of vomiting after tonsillectomy was similar to that observed in previous investigations,[4 5 8] but greater than that reported by van den Berg.[9] Although both drugs decreased the incidence of vomiting compared with placebo, the incidence of emesis after prophylactic treatment was still high in this study. Ideally, the incidence of vomiting should be less than the 41% rate noted. Also, a decrease in the use of rescue antiemetics and elimination of the instances where children have numerous episodes of vomiting would be desirable. In addition, the incidence of vomiting on the day after surgery (25–26%) is of concern.

We used a blocked, stratified design to permit both control and flexibility. Patients were enrolled into this study before the parents and their child's anaesthetist had come to a decision as to premedication and the anaesthesia induction technique. The blocked and stratified approach leads to a balanced design, which simplifies inter-group comparisons, while flexibility in choice of premedication and induction technique optimizes clinical management.

Adverse effects with a single, therapeutic dose of ondansetron or perphenazine are extremely rare and generally minor. In Desilva and colleagues's study in adults,[6] only patients who received perphenazine were free of adverse side effects. Perphenazine is a phenothiazine, a class of drugs which have a high therapeutic index and "are remarkably safe agents".[10] Major adverse side effects after a single dose of ondansetron are rare, and there is only one report of dyskinesia after a single dose of perphenazine.[11] Although there were no adverse events caused by perphenazine during this and previous studies,[5 12] much larger sample sizes would be required to evaluate accurately the incidence of adverse effects after perphenazine in children.

The prophylactic antiemetics used in this study were dissimilar with respect to cost. The ondansetron dose for a 20-kg child (3 mg) costs $12.90 Canadian, while perphenazine costs only $0.81 Canadian for the treatment of a 20-kg patient. Treatment of emesis by nursing staff and family, delayed hospital discharge, unscheduled admission and mental costs to the patient and family also add to the cost of care. Of note, in this study those patients in the perphenazine-treated group had a slight delay in discharge (7 min) from the day-case surgical unit compared with the ondansetron group. Unfortunately, we are not able to calculate the cost of such delays within our health care system.

The dose of perphenazine was based on the 5-mg dose used in adult investigations. A larger dose (8 mg) has been noted to increase drowsiness among adult oncology patients.[13] There are, to the best of our knowledge, no dose–response curves for the antiemetic effect of this drug in the perioperative setting in adults or children. While the dose used in our study has been shown previously to be effective, it is not necessarily the optimal dose. The ondansetron dose is based on previous studies in children in a perioperative setting.[4 14]

The aetiology of vomiting after tonsillectomy is unknown and probably multifactorial in origin. Surgical techniques which minimize blood loss may be as effective as the use of antiemetics in attempting to decrease vomiting after tonsillectomy.

The sex of the child was identified as a significant predictor of postoperative vomiting by logistic regression analysis. This is, to the best of our knowledge, the first report that male children vomit more than female children after anaesthesia–surgery and is probably a spurious finding. It is not expected that future studies will support this observation. With almost identical male to female ratios in the two study groups, the difference in vomiting according to the child's sex had no effect on our results.

In summary, ondansetron and perphenazine had similar effects on vomiting in children after tonsillectomy. However, the observed incidence of vomiting was unacceptably high (41–44%), especially on the day after surgery (25–26%).

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Effects of preinduction and intraoperative warming during major laparotomy†

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Summary

We have investigated the influence of active warming before and during operation on blood loss, transfusion requirements, duration of stay in the post-anaesthesia care unit (PACU) and perioperative costs in 40 patients undergoing major abdominal surgery. Patients were allocated randomly to one of two groups: in the study group ($n = 20$), patients were actively warmed using forced air for 30 min before induction of general anaesthesia and during anaesthesia. Passive protection against heat loss consisted of circulating water mattresses, blankets and fluid warming devices, and was used both in the active warming group and in the control group ($n = 20$). At the end of surgery the change in core temperature was significantly less in the group of actively warmed patients (0.5 (SD 0.8) °C *vs* 1.5 (0.8) °C; $P \leq 0.01$). Blood loss and transfusion requirements were less in the actively warmed patients, who had a shorter duration of stay in the PACU (94 (SD 42) min *vs* 217 (169) min; $P \leq 0.01$) and a 24 % reduction in total anaesthetic costs. (*Br. J. Anaesth.* 1998; **80**: 159–163)

Keywords: surgery, abdominal; hypothermia; temperature, effects; temperature, monitoring; equipment, warming devices

Central body temperature decreases after induction of general anaesthesia as a result of reduced metabolic heat production and redistribution of heat from the central to peripheral compartments.[1] During laparotomy, heat loss may also be increased because the large surface of the intestine is exposed to the relatively cold environment of the operating room. These findings are relevant because intraoperative hypothermia is associated with an increased rate of postoperative myocardial ischaemia,[2] increased plasma concentrations of catecholamines[3] and an increased rate of postoperative wound infection.[4] Moreover, in patients undergoing total hip replacement, blood loss and transfusion requirements were reduced when central body temperature was kept normal.[5]

During hip arthroplasty, intraoperative hypothermia was prevented by preoperative warming with an electric warming blanket for 90 min.[6] Heat loss in the central body compartment after induction of general anaesthesia may be minimized by active warming of the arms and legs for 30 min.[7] Conflicting results on the effect of central body temperature on duration of stay in the post-anaesthesia care unit (PACU) have been reported.[8 9] As these findings imply that hypothermia may be associated with increased perioperative costs, we investigated if warming for 30 min before induction of anaesthesia combined with intraoperative warming with forced air prevents hypothermia during major abdominal surgery. Additionally, intraoperative blood loss, time to discharge from the PACU and total costs of perioperative management were compared with a control group who received conventional treatment of hypothermia, consisting of fluid warming devices, circulating water mattresses, cotton blankets and postoperative radiant warming.

Patients and methods

After obtaining approval from the local Ethics Committee and written informed consent, we studied 40 patients undergoing major abdominal surgery, allocated randomly to receive either passive isolation against hypothermia with fluid warming devices, circulating water mattresses, two layers of blankets and postoperative radiant warming, or additional active warming of the upper body using forced air, beginning 30 min before induction of general anaesthesia and during anaesthesia.

During a 1-yr period from November 1995 until October 1996, ASA I–III patients undergoing major abdominal surgery for cancer or inflammatory bowel disease were included. In one additional patient, a gastrojejunostomy was performed because of annular pancreas (table 1). All surgical procedures were performed via a median laparotomy, and surgery lasted for more than 2 h. Patients undergoing surgery of the biliary tract, liver, pancreatic surgery or gastrectomy were excluded, as were those who underwent preoperative radiotherapy or suffered from recurrent rectal cancer because of the greater risk of blood loss. No patient showed signs of bowel obstruction or acute onset of inflammatory bowel disease. Patients did not suffer from diabetes mellitus, thyroid disease, autonomic dysfunction, Cushing's syndrome, peripheral

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Table 1 Surgical procedures in the two groups (*n*)

	Active warming	Control
Major colonic resection	17	17
Intestinal resection	1	2
Pancreaticojejunostomy	1	0
Duodenojejunostomy	1	0
Retroperitoneal lymphadenectomy	0	1

vascular disease, platelet dysfunction or any other coagulopathy, or had a history of smoking more than 20 cigarettes per day for more than 5 yr or treatment for arterial hypertension. Patients' weights were within 20% of ideal body weight. On arrival in the preoperative holding area, tympanic membrane temperature was measured, and patients with a temperature greater than 37.5 °C or less than 36.5 °C were excluded.

STUDY DESIGN

Passive prevention of hypothermia included covering the patient's body and extremities with two layers of blankets and the use of circulating water mattresses (temperature set at 39 °C) and fluid warming devices for infusions. Active warming was provided by the Warm Touch System (Mallinckrodt Medical GmbH, Hennef/Sieg, Germany) set at the highest flow rate and in the temperature range 40–42 °C. When the system switched to the range below this, the temperature of the forced air was reset to 40–42 °C. Ambient room temperature was maintained at approximately 22 °C during the preinduction period and during anaesthesia.

On the evening before surgery, the bowel was cleaned with a standard electrolyte solution. Ten minutes before arrival in the holding area, patients were premedicated with midazolam 7.5 mg orally. After haemodynamic and temperature monitoring had been established, the patient's abdomen and legs were covered with two layers of blankets. The arms and chest of those patients receiving preoperative active warming were warmed using forced air, whereas in the control group the arms and chest were covered with blankets. Thirty minutes later, general anaesthesia was induced with fentanyl 2–4 $\mu g\ kg^{-1}$, thiopental 3–5 mg kg^{-1} and atracurium 0.5 mg kg^{-1} or cisatracurium 0.1 mg kg^{-1}. The trachea was intubated, a central venous catheter was inserted into the right internal jugular vein and a 14-gauge cannula into a forearm vein. Warmed fluids were provided via this cannula. The central venous catheter was used for drug administration and for measurement of central venous pressure. When considered necessary, a 20-gauge cannula for continuous measurement of arterial pressure was inserted into the right radial artery. Anaesthesia was maintained using fentanyl, isoflurane (maximum end-tidal volume 1.0 MAC) and nitrous oxide in 70% oxygen. Fresh gas flow was kept constant at 3.0 litre min^{-1}.

Fluid replacement was guided by central venous pressure. A core temperature of less than 35 °C or significant peripheral vasoconstriction for more than 2 h were judged as criteria for maintaining mechanical ventilation after operation. The criteria for tracheal extubation after mechanical ventilation in the PACU were: central body temperature >36.0 °C, absence of significant peripheral vasoconstriction, and heart rate and arterial pressure within ± 20% of baseline. In the postoperative phase, radiant heat was used to rewarm hypothermic patients.

MEASUREMENTS

Arterial pressure was measured non-invasively via oscillometry; in a few patients it was also recorded via invasive arterial pressure measurement when indicated medically. An electronic thermocouple (Mallinckrodt Medical) was used to record tympanic membrane temperature, which was considered to reflect central body temperature.[1] Skin surface temperatures were measured by thermocouples placed on the middle of the forearm and on the tip of the ipsilateral middle finger; temperatures were obtained from the arm that was not used for indirect measurement of arterial pressure. A difference between central and peripheral temperatures of more than 4.0 °C was considered to indicate significant vasoconstriction.

During operation, arterial pressure, heart rate, peripheral oxygen saturation, end-tidal carbon dioxide and isoflurane concentrations, and temperatures were recorded at 15-min intervals. Central venous pressure was measured at 30-min intervals, and central venous or, if available, arterial blood-gas samples were obtained every 60 min. After operation, temperatures were recorded at 30-min intervals until normothermia was achieved. On arrival in the PACU, blood samples were obtained for coagulation tests and blood cell counts, and to measure blood-gas tensions and serum concentrations of electrolytes, creatinine and urea. Laboratory analyses were repeated on the first postoperative day. For analysis of arterial and central venous blood-gas tensions, the Ciba Corning 288 (Ciba Corning, Fernwald, Germany) analyser was used.

Blood loss was estimated by an independent anaesthetist who was not involved in the study and who took care of the patient during surgery or during the patient's stay in the PACU. The indication for transfusion of packed red blood cells or fresh frozen plasma was confirmed by the supervising staff anaesthetist who was also not involved in the study. Thus the anaesthetist in charge was always blinded to the fact that the amount of blood loss and transfusion requirements were part of the study. The presence or absence of shivering was determined by the anaesthetist in charge on the PACU who was blinded to the study. The time the patient was ready to be discharged from the PACU was set retrospectively by a blinded observer using a modified Aldrete and Kroulik scoring system.[10] A core temperature of more than 36.0 °C and a score of 14 points was regarded as a criterion for discharge (table 2).

The costs of perioperative management were calculated with respect to the salaries and costs for the University of Heidelberg in August 1996. For preinduction warming, we calculated a nurse-to-patient ratio of 1:4; the costs of treating patients in the control group before induction of anaesthesia were calculated as zero. During surgery, an anaesthetist-to-patient ratio of 1:1 and a nurse-to-patient ratio of 1:2 was assumed. In the PACU, the anaesthetist-to-patient ratio was 1:10. For a patient who required

Table 2 Criteria for discharge from the PACU. Central body temperature had to be >36.0 °C

	Zero point	One point	Two points
Activity	No movement	No purposeful movement	Correct movement on command
Respiration	Apnoea	Dyspnoea or limited breathing	Breathes deeply and coughs freely
Supplementary O_2 required to maintain Sa_{O_2} >95% (litre min^{-1})	>5	2–5	<2
Consciousness	Unresponsive	Arouses to verbal stimuli	Fully awake
Arterial pressure	AP > or <50% of baseline	AP 20–50% of baseline	AP 0–20% of baseline
Heart rate (beat min^{-1})	<45 or >120	45–49 or 101–120	50–100
Gastrointestinal tract	Severe vomiting	Vomiting within 30 min	Little or no vomiting
Renal function	Anuria	≤0.3 ml kg^{-1} h^{-1}	>0.3 ml kg^{-1} h^{-1}

Table 3 Patients' characteristics (mean (SD or range) or number). No difference between groups

	Active warming	Control
Age (yr)	43 (19–67)	49 (27–78)
Sex (F/M)	10/10	9/11
Height (m)	175 (8)	171 (9)
Weight (kg)	73 (14)	72 (14)
Length of operation (h)	4.0 (1.4)	4.3 (1.6)
Fentanyl (µg kg^{-1} h^{-1})	3.0 (1.0)	3.6 (1.5)
Intraoperative volume (ml)	982 (220)	1224 (273)

mechanical ventilation in the PACU, the nurse-to-patient ratio was regarded as 1:1, and for a spontaneously breathing patient in the PACU it was 1:3. A cost of £14.30 sterling was calculated for an upper body layer of the Warm Touch System. No costs were calculated for the ventilator of the Warm Touch System or for the radiant heater because both devices were already present in our department. The costs calculated for each patient comprised the salaries for the anaesthetist and nurse assisting him and the costs for anaesthetic equipment, such as venous catheters, tracheal tubes, etc., and the medical treatment the patient required. The costs for isoflurane and nitrous oxide were not taken into consideration. An exchange rate of £1 to 2.8 German marks was assumed for calculation of perioperative costs.

DATA ANALYSIS

Time-dependent results were evaluated using analysis of variance (ANOVA) with *post hoc* Scheffé's test. Results in the two treatment groups were compared by unpaired, two-tailed *t* tests. Data are presented as mean (SD).

Results

Patient characteristics, duration of surgery and anaesthetics are given in table 3. There were no differences between the two groups. After operation, one patient in the control group was admitted to the intensive care unit which was not controlled by anaesthetists. Consequently, this patient was excluded from the calculation of perioperative costs. Duration of stay in the PACU was not investigated in this patient because postoperative treatment differed.

Before operation, central body temperature was not altered in either group. During the preinduction period, central body temperature did not differ significantly between the two groups. From 15 min after intubation until the end of surgery, central body temperature was higher in the prewarmed group ($P \leq 0.01$) (fig. 1) and remained higher in this group for the first 180 min after arrival in the PACU ($P \leq 0.01$ for the first 150 min; $P \leq 0.05$ for the following 30 min). At the end of surgery and during the first hour in the PACU, 12 of 20 patients in the control group showed significant vasoconstriction, whereas vasoconstriction was detectable in only four of 20 patients in the prewarmed group. On arrival in the PACU, seven patients in the control group showed signs of shivering, and six additional patients underwent mechanical ventilation because of hypothermia. In all patients in the prewarmed group, the trachea was extubated immediately after surgery. Only one of these patients showed shivering in the PACU.

Intraoperative blood loss was significantly less in the normothermic group (635 (507) ml *vs* 1070 (803) ml; $P \leq 0.05$). During operation, only one patient in the study group received 2 u. of packed red blood cells, while in the control group six patients received blood products. By the morning after surgery, packed red blood cells or fresh frozen plasma had been transfused to two study patients. However, a total of nine control patients received blood products by the first morning after surgery. Expressed in millilitre per patient, warmed patients were given significantly less blood products on admission to the PACU (30 (134) *vs* 240 (432) ml/patient; $P \leq 0.05$) and by the morning after surgery (95 (293) *vs* 502 (754) ml/patient; $P \leq 0.05$).

There were no significant differences in partial thromboplastin time or prothrombin time between the two groups before operation, on admission to the PACU, 12 h after operation or on the first morning after operation. Among warmed patients, platelet count decreased from 303 000 (100 000) µl^{-1} before operation and 296 000 (109 000) µl^{-1} on admission to the PACU, to 266 000 (60 000) µl^{-1} 12 h after the end of operation. On the morning after surgery, platelet count was 234 000 (80 000) µl^{-1} in this group. In the control group, platelet count decreased from 288 000 (83 000) µl^{-1} before operation and 257 000 (77 000) µl^{-1} to 218 000 (54 000) µl^{-1} 12 h after operation and remained constant for the next 24 h. There was no significant difference between the two groups, but using a two-tailed paired *t* test, the level of significance was 0.065 at 12 h after operation.

After 94 (42) min, prewarmed patients were ready to be discharged from the PACU compared with 217 (169) min in the control group ($P \leq 0.01$). The costs of treatment from the beginning of preinduction warming until discharge from the PACU were £408 (105) for an aggressively warmed patient and £534 (250) for a control patient ($P \leq 0.05$). Thus 24% of the costs for the anaesthetic treatment could be saved by maintenance of normothermia. Preinduction warming contributed to 4.6 (1.3)% of total costs.

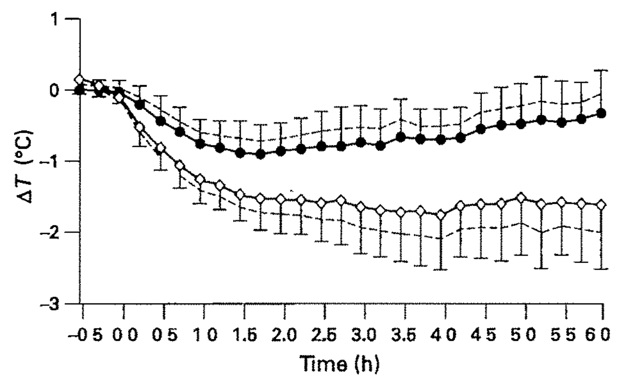

Figure 1 Change in core temperature (ΔT) during the preinduction period and anaesthesia in the actively warmed patients (closed symbols) and in the control group (open symbols). Time zero = induction of general anaesthesia. Data are mean (SD) (95% confidence interval of the mean). $P < 0.01$ from 0.25 h to 6 h.

Discussion

Our major finding was that maintenance of normothermia reduced the total costs for anaesthetic treatment overall by 24% during major abdominal surgery. This was mainly because of a shortened stay in the PACU, lower incidence of postoperative mechanical ventilation and reduced perioperative blood loss, resulting in fewer transfusion requirements in normothermic patients.

Our study supports the findings of Schmied and co-workers on the effect of core hypothermia on blood loss and transfusion requirements during total hip arthroplasty.[5] We did not include such a detailed haemodilution and transfusion procedure in our study because much greater blood loss could be tolerated by the younger patients undergoing abdominal surgery. In common with Schmied and co-workers,[5] we did not observe any significant differences in prothrombin time or partial thromboplastin time between groups. One reason might be that the laboratory investigations were performed at a temperature of 37 °C and a reversible coagulopathy induced by hypothermia may only be detected when clotting tests are performed at the patient's central body temperature.[11] [12] In contrast, some patients received fresh frozen plasma in the control group when coagulopathy was observed clinically, whereas among normothermic patients fresh frozen plasma was not given. The assumption that hypothermia produces a clinically relevant coagulopathy in abdominal surgery was also supported by a study on the effects of hypothermia on wound infection and duration of hospitalization.[4] Normothermic patients required less units of red blood cells than hypothermic patients during abdominal surgery lasting approximately 3 h. In our study, normothermic patients had a slight, but non-significant, higher platelet count 12 h after operation. This may also indicate a clinically relevant coagulopathy in hypothermic patients.

In contrast with our results, hypothermia was found to have no influence on duration of stay in the PACU in children recovering from peripheral surgery.[8] However, that study was not randomized, and patients and surgical procedures were different from those in our investigation. The assumption that hypothermia prolongs post-anaesthetic recovery has recently been proved in a randomized prospective study[9] which concurs with our data. Unlike this investigation, we included central body temperature as a criterion for fitness of discharge from the PACU, as some hypothermic patients underwent mechanical ventilation when they arrived in the PACU. In contrast with the study by Lehnhardt and co-workers[9] however, hypothermia was treated after operation in our study.

The estimated salary of a nurse taking care of four patients in a holding area and the cost of the upper body layer of the Warm Touch System contributed to 4.6% of the costs of total perioperative anaesthetic management during the day of surgery. Considering all aspects, however, the costs of perioperative management for each patient were significantly lower in the actively prewarmed group. Thus the 24% reduction in costs for each actively warmed patient represents a large economic impact compared with the cost of approximately £1430 for the ventilator of an active warming device. These results are new and have been confirmed only indirectly by other studies which showed complications associated with mild intra- and postoperative hypothermia. Thus maintenance of intraoperative normothermia has been shown indirectly to reduce the costs of hospitalization by incurring a lower incidence of wound infections and a shorter duration of hospitalization,[4] shorter duration in the PACU,[9] reduced transfusion requirements[5] and a lower incidence of myocardial ischemia.[2] However, our study is the first to have directly evaluated the economic benefits of intraoperative normothermia for an anaesthesia department.

The reduction in total costs of perioperative treatment of a single patient produces an economic benefit for the anaesthetic department as a whole. This would appear to contradict a computer simulation of economic management of a PACU.[13] In that investigation, the distribution of admissions to PACU was found to be the major determinant of PACU costs, whereas the time of fitness for discharge was of minor economic importance. However, in that analysis, the PACU investigated was solely for outpatients, that is those recovering from minor surgery. Our PACU, however, provides care for patients recovering from outpatient surgery and for those undergoing major abdominal or vascular surgery, including the opportunity for postoperative mechanical ventilation. The costs of supplies, medication and transfusion products are thus likely to be higher in our PACU than in a PACU for outpatient surgery where they contribute to only 2% of the total costs.[13] However, the costs of loans are also the major determinant for the total costs in our PACU. Contrary to the study by Dexter and Tinker,[13] our PACU is also used during the night. Thus a smaller number of nurses have to work during the night shift in our PACU if patients are ready to be discharged earlier in the evening after maintenance of perioperative normothermia.

In summary, maintenance of intraoperative core normothermia helped to reduce blood loss and save blood products. Furthermore, duration of stay in the PACU was prolonged in hypothermic patients, even though hypothermia was treated in the PACU. The costs of perioperative management were lower in patients who remained normothermic although they had to be supervised during the preinduction warming period.

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Relationship between cardioventilatory coupling and respiratory sinus arrhythmia

D. C. GALLETLY AND P. D. LARSEN

Summary

Recent studies have suggested a role for respiratory sinus arrhythmia in improving pulmonary gas transfer. However, the physiological role of cardioventilatory coupling is unknown. We have tested the hypothesis that cardioventilatory coupling aligns heart beats at positions of the ventilatory cycle where they are maximally affected by respiratory sinus arrhythmia (RSA). In 15 anaesthetized, spontaneously breathing subjects, we recorded continuously the timing of inspiration and the ECG. We then plotted the change in RR interval which occurred, as a result of RSA, after onset of inspiration (RSA plot). By comparing these RSA plots with the distribution of heart beats during the ventilatory cycle, we were able to examine the positioning of heart beats relative to acceleration of heart rate as a result of RSA. In all but two subjects we observed that during periods of strong cardioventilatory coupling, heart beats occurred at positions in the ventilatory cycle where they were maximally affected by RSA. In the presence of strong coupling, the shortest possible RR interval occurred during late inspiration, the longest possible RR interval occurred immediately before the start of inspiration. We suggest that cardioventilatory coupling may have a physiological role in optimizing RSA, perhaps to improve cardiopulmonary performance during sleep. (*Br. J. Anaesth.* 1998; **80**: 164–168)

Keywords: heart, heart rate; heart, arrhythmia; monitoring, electrocardiography; cardiorespiratory system, effects

Respiratory sinus arrhythmia (RSA) is the variation in heart beat interval with respiration. Since its description by Carl Ludwig in 1847 the mechanism of RSA has been the subject of considerable research interest. Currently it is believed that RSA results from modulation of vagal efferent activity to the cardiac sinus node through gating of excitatory input to the vagal motor neurones from lung inflation afferents.[1] Inspiration is accompanied by vagal withdrawal and a corresponding increase in heart rate, expiration is accompanied by increased vagal tone and a decrease in heart rate. The magnitude of RSA varies according to the degree of vagal tone and may be reduced by standing, age and administration of drugs which interfere with muscarinic cholinergic receptors.[2]

A separate interaction between heart beats and respiration is cardioventilatory coupling (CVC), an entrainment phenomena in which ventilation and heart beats become synchronized in whole number ratios and heart beats appear to fall in constant timing relationship with inspiratory onset. Coupling is seen best under conditions of low arousal: sleep, sedation and general anaesthesia. The synchronization of gill movements to heart beats was first described in fish by Schoenlein in 1895,[3] the coupling of ventilation to heart beats in mammalian species by Coleman in 1921[4] and in humans by Galli in 1924.[5]

The mechanism of CVC is thought to be triggering of inspiratory timing by arterial or intracranial pressor receptor afferents.[5] Unlike RSA which is the modulation of cardiac timing by pulmonary afferent information, CVC is a modulation of inspiratory timing by haemodynamic afferent information.

Despite their important effects on governing the interaction between breathing and heart rate, the link between CVC and RSA is not known. However, as coupling aligns inspiratory onset to heart beats, then it must also position heart beats where they are subjected to varying degrees of vagal modulation from RSA. Although the physiological role of CVC is not known, there is a general belief that RSA may help stabilize cardiovascular variables in the face of fluctuating intrathoracic pressure[6] and recent work suggests that it may improve pulmonary oxygenation.[7] If RSA has a role in improving cardiopulmonary performance, then the positioning of heart beats where they are maximally affected by RSA could have some physiological benefit. In this study, we have examined the hypothesis that CVC aligns heart beats relative to inspiratory onset such that the inter-beat interval is maximally affected by RSA.

Patients and methods

After obtaining Ethics Committee approval, we obtained data from 20 consenting, adult patients undergoing elective surgical procedures under general anaesthesia. None was receiving regular medications or had evidence of cardiorespiratory disease.

Anaesthesia was induced with propofol 2–2.5 mg kg^{-1} and maintained by spontaneous inhalation of 1–1.5% isoflurane and 66% nitrous oxide in oxygen. After induction, a laryngeal mask airway was

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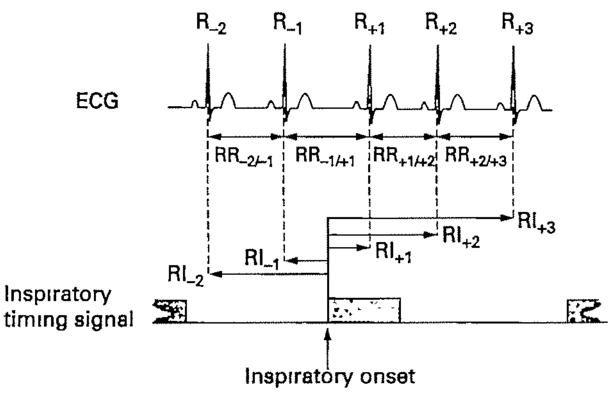

Figure 1 Schematic representation of ECG and inspiratory timing signals. From these signals the time interval from the R wave to the following onset of inspiration (RI_{-1}, RI_{-2}) and the preceding onset of inspiration (RI_{+1}, RI_{+2}, RI_{+3}) are calculated. The R waves of the ECG are denoted relative to the onset of inspiration. R waves preceding inspiration are designated negative subscripts (thus R_{-1} is the R wave immediately before onset of inspiration). R waves after inspiration are given positive subscripts (thus R_{+1} is the R wave immediately after inspiration). RR intervals are denoted by the subscripts of the two bounding R waves: $RR_{-1/+1}$ is the RR interval between the R wave which immediately precedes inspiration to the R wave which immediately follows.

inserted. The last 10 patients received an opioid to aid mask insertion: five received fentanyl 50–100 µg and five morphine 5–10 mg. All data recordings were made after opioid administration but before the onset of surgery.

We recorded continuously the ECG (lead CM_5, Corometrics Neo-Trak 502) and the timing of inspiratory onset. Inspiratory timing was measured by incorporating a Ruben non-return valve into the anaesthetic breathing system. The valve was modified by addition of a photodetector and light beam across the path of the valve shuttle which generated a 1.5-V square wave signal while the valve was open (from the start of inspiration to the end of inspiration). Using this method of inspiratory timing, a small delay may be expected from the onset of inspiratory airflow until opening of the valve shuttle. Measured inspiration therefore falls a little after true inspiratory onset and this delay may vary depending on inspiratory flow patterns. As this delay is small however and equally affects the RSA curve, RI_{+1} and RI_{+2} (see below), and by confining analysis of these measurements to within-subject comparisons, we believe the delay is unlikely to affect the conclusions of our study.

For a minimum of 20 min, ECG and photodetector output were recorded using a 16-bit ADC board (NB-MIO-16, National Instruments), on a Macintosh IIcx personal computer at a sampling rate of 500 Hz.

ANALYSIS

Cardioventilatory coupling

Cardioventilatory coupling was assessed by measuring the time of each R wave peak from the ECG and the time of each inspiratory onset. We then determined the time interval between each R wave and the immediately following, and preceding, inspiratory onset (RI intervals). RI intervals and R waves for heart beats preceding the inspiration were given a negative subscript and those after inspiration were given a positive subscript: R_{-1} for the beat preceding the inspiration and R_{+1}, R_{+2} etc for consecutive beats after inspiration. RR intervals were given a subscript according to the their bounding R waves: $RR_{-1/+1}$ for the interval between R_{-1} and R_{+1}. This nomenclature is explained in figure 1. $RI_{\pm}$ intervals were plotted against time of R wave occurrence (RI plot). Coupling of heart beats and ventilation is revealed in these plots as horizontal banding, in which values of $RI_{\pm}$ remain constant over time.

Because the degree and pattern of cardioventilatory coupling varies in any individual over time,[8] RI plots commonly show periods of poor coupling where heart beats occur in no fixed relationship to inspiratory onset and periods of stronger synchronous coupling where heart beats occur, to varying degrees, in constant timing relationship to inspiratory onset. In part, this patterning varies according to the degree to which heart rate and ventilatory rate are in whole number ratio.

RSA plots

Shortening of RR interval, which occurs after the onset of inspiration as a result of RSA, was displayed graphically by plotting, for each R wave, the normalized preceding RR interval (duration of the preceding RR interval divided by the mean RR interval; the mean being calculated empirically from a window 10 beats on each side of the interval under examination) against the time at which that heart beat decreased after the onset of inspiration. Mean values of normalized RR were then obtained for each 0.1-s interval after inspiratory onset and the curve of respiratory sinus arrhythmia (RSA plot) constructed by interpolating these points. These RSA plots were established from those portions of the RI time series in which coupling was least apparent (weak or absent coupling), during which time heart beats occurred at all phases of the ventilatory cycle and the full extent of the RSA curve could be seen. From these plots we then measured the time from inspiratory onset to: (a) the time at which RR interval acceleration began; and (b) the nadir of the RSA curve (fig. 2).

From segments of the RI plot which showed strongest coupling (heart beats and ventilations were in reasonable synchrony for periods of longer than 50 breaths) we constructed histograms of R wave distribution after inspiratory onset. We then superimposed these plots and the previously constructed RSA plots to determine where, within the RSA curve, groupings of heart beats occurred during cardioventilatory coupling (fig. 3). The mean time to these R wave groupings from inspiratory onset (RI_{+1}, RI_{+2} ....) was calculated and compared with the onset of acceleration and nadir points of the RSA curve.

All data acquisition and raw data analysis were performed using software developed in LabView 2 (National Instruments) and purpose written by the authors. Statistical analysis was performed using Statview 4 on a Macintosh LCIII personal computer.

Results

Of the 20 subjects, 15 had RI plots suitable for analysis (six males, nine females, mean age 30.7 (range

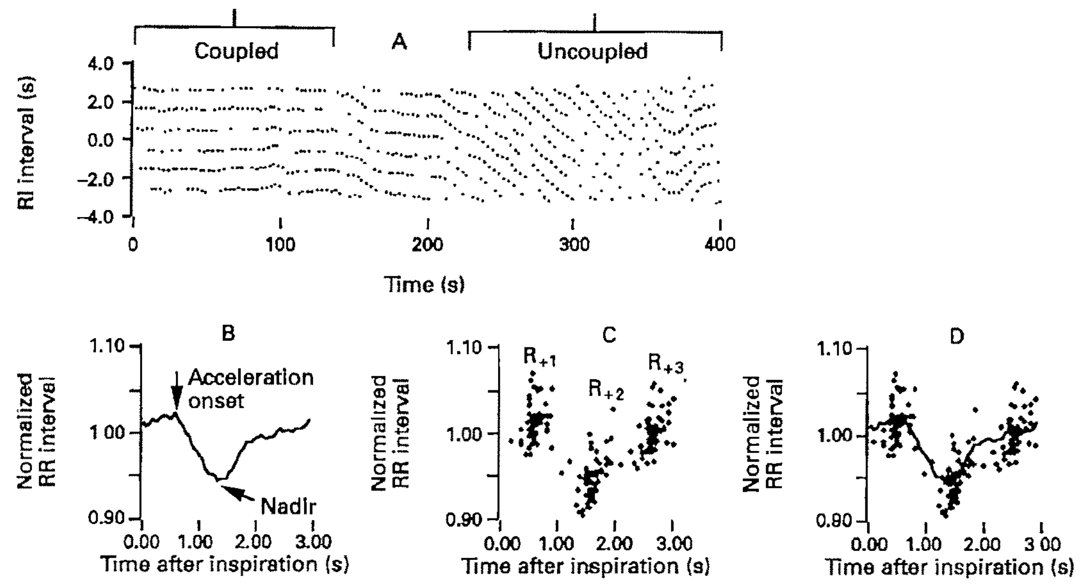

Figure 2 A: Representative example of an RI interval time series showing a segment (0–140 s) of strong cardioventilatory phase coupling during which time heart beats occurred in constant relationship to inspiratory onset, and a weakly coupled segment in which heart beats occurred at all phases of the ventilatory cycle (220–400 s). B: Mean value of the normalized, preceding RR interval (RR interval/mean RR) for time periods after inspiratory onset (RSA curve) was determined from the weakly coupled segment. Acceleration onset and nadir were measured. C: Normalized RR values for intervals derived from the strongly coupled segment show grouping of RR intervals as a result of the timing relationship between R waves and inspiratory onset. D: Superimposition of plots B and C demonstrates that the heart beat grouping R_{+1} has fallen at the acceleration onset of the RSA curve and has therefore been preceded by the longest possible RR interval, and that the R_{+2} grouping has fallen at the RSA nadir and has therefore been preceded by the shortest RR interval for that RSA curve.

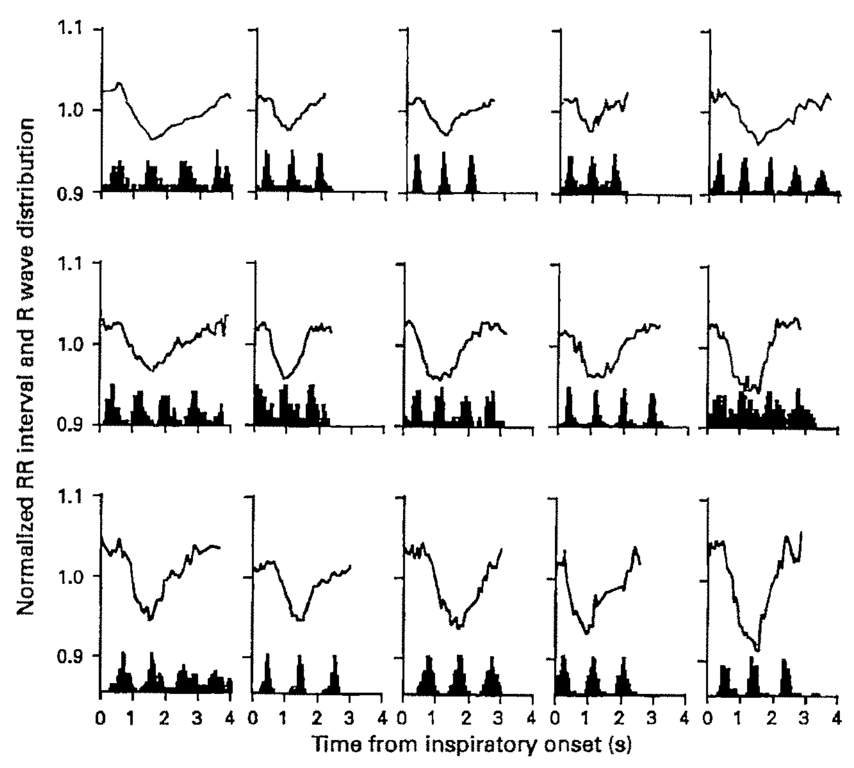

Figure 3 For each subject the figure shows the RSA curve (normalized preceding RR interval *vs* time after inspiration) for weakly coupled segments and histograms of R wave distribution during strong coupling. Note the concordance between the first R wave grouping (R_{+1}) and acceleration onset, and the concordance between the second R wave grouping (R_{+2}) and nadir of the RSA curve.

18–62) yr; nine received an opioid, five morphine, four fentanyl). In the remaining five subjects, the degree of coupling remained constant throughout the recording period and no clear separation between periods of strong and weak or absent coupling were obtained.

From the 15 suitable recordings, during periods of weak or absent coupling, the scattered distribution of heart beats throughout the ventilatory cycle allowed RSA plots to be obtained, all subjects showing the expected heart rate acceleration after inspiratory onset. The nadir of the RSA curve (i.e. the time of an

R wave which has been preceded by the shortest possible RR interval) varied between subjects, with a mean time from inspiratory onset of 1.35 (SD 0.32) s. The onset of acceleration (i.e. the time of an R wave which has been preceded by the longest possible RR interval) occurred at a mean time of 0.43 (0.23) s after inspiratory onset.

Data epochs used for establishing the RSA curve and strongly coupled R wave groupings were not significantly different with regard to mean RR interval (0.896 *vs* 0.893 s; P=0.95, paired t test) or ventilatory frequency (20.2 *vs* 19.7 bpm; P=0.76, paired t test).

RSA plots from strongly coupled segments all showed clustering of heart beats at discrete time intervals after inspiratory onset. Superimposition of these strongly coupled R wave groupings and the previously constructed RSA curves (fig. 2) showed that during strong coupling, the heart beats corresponding to the R_{+1} and R_{+2} groupings generally occurred on, or close to, the acceleration onset and nadir of the RSA curve, respectively. The distribution of heart beats and corresponding RSA plots for all subjects are shown in figure 3. The mean RI_{+2} for strongly coupled beats was not significantly different from the time to RSA nadir (RI_{+2} 1.29 (0.22) s (95% confidence intervals (CI) 1.18–1.40) *vs* nadir 1.35 (0.32) s (95% CI 1.19–1.50); P=0.22, paired t test). Power analysis indicated that there was an 80% probability of a difference of 10% or greater being found statistically significant. Similarly, RI_{+1} was not significantly different from the acceleratory onset of the RSA plot (RI_{+1} 0.418 (0.16) s (95% CI 0.340–0.497) *vs* acceleration onset 0.429 (0.23) s (95% CI 0.314–0.544); P=0.94, paired t test).

Time from inspiratory onset to R_{+1} showed a significant positive correlation with time to the start of acceleration of the RSA curve (r=0.63, $P < 0.01$). Time to nadir and mean RI_{+2} were also positively correlated (r=0.85, P<0.0001). Thus as R wave groupings shifted with changes in heart rate, so also did the reference points on the RSA plot.

Discussion

The observations in this study link the timing of CVC to that of RSA suggesting that, during coupling, heart beats are positioned in such a way that vagal modulation of RSA is maximized. In the absence of CVC, heart beats occur at random positions within the RSA curve and are subjected to varying degrees of vagal modulation. Less inspiratory acceleration of RR interval might be expected if heart beats occur at the sides of the RSA curve. In the presence of CVC however, heart beats were generally subjected to the maximal effects of RSA. $RR_{+1/+2}$ was the shortest possible interval for that RSA curve implying the greatest degree of vagal withdrawal. $RR_{-1/+1}$ was the longest possible interval implying that, during strong coupling, vagal withdrawal at the cardiac sinus pacemaker begins to occur only after the R_{+1} heart beat.

Any putative optimization of RSA by CVC implies a physiological benefit from these processes. Whether the relationship between RSA and phase coupling is simply fortuitous however, or the result of evolutionary design remains open to question. Demonstration of this relationship strengthens the case for their having some physiological significance. A commonly held view with regard to RSA is that it compensates for the haemodynamic effects of varying intrathoracic pressure with ventilation, perhaps matching cardiac output to the variation in venous return or reducing the fluctuations in mean arterial pressure.[6] Evidence for this haemodynamic benefit is poor and an alternative hypothesis has been put forward recently with the demonstration, in dogs, that in contrast with the condition where RSA is absent, artificially induced RSA had no effect on cardiac output, but significantly improved pulmonary oxygenation: reducing the ratio of physiological deadspace to tidal volume, decreasing shunt fraction and increasing oxygen uptake.[7] The mechanism of this effect may be a simple reduction of the time over which blood is replaced within pulmonary capillaries when alveoli are filled with fresh gas, and a lengthening of blood replacement time towards the end of expiration when $\dot{V}/\dot{Q}$ mismatch is more likely and the alveoli are filled with gas of reduced $P\text{A}_{O_2}$ and increased $P\text{A}_{CO_2}$.

Alone, RSA would be unable to achieve synchronization of heart beat timing to ventilation as heart beat timing is determined by the independent sinus pacemaker which is only slowed or accelerated by vagal activity. By triggering inspiration from baroreceptor afferents however, heart beats can be made to occur in exact relationship with the inspiratory period. Thus in the presence of coupling, the shortest possible RR interval and hence pulmonary capillary transit time occurs as the alveoli are filling with fresh gas. The longest RR interval and capillary transit time occur at the end of the ventilatory cycle when the alveoli are filled with "stale" alveolar gas. Although this effect may have little significance for well ventilated areas of the lung, it may become important in those areas where ventilation is low relative to perfusion or in those subjects where FRC approaches closing volume.

If pulmonary gas exchange is improved by RSA and this in turn is optimized by CVC, then this would be consistent with the conditions under which RSA and coupling are known to occur. It is well recognized that sleep, sedation and general anaesthesia, and the accompanying supine posture, may be associated with impaired ventilation, gas exchange and reduced functional residual capacity. Under normal physiological conditions, coupling is best seen during sleep.[3] Sinus arrhythmia is also of greatest amplitude during sleep and in the supine posture because of increased vagal tone.[3 9] It is therefore possible that these mechanisms act to reduce the effects of sleep or supine posture, or both, on disordered gas exchange. It is also perhaps of note that both RSA and phase coupling occur less frequently in REM sleep than in non-REM and this may explain in part why REM sleep is associated with poorer gas exchange than non-REM sleep.

In this study, in order to maximize the accuracy of data collection, we have used data from patients undergoing general anaesthesia. Anaesthesia is plainly a non-physiological state, and the degree of RSA may be altered by the effects of anaesthetic agents and adjuvants.[10] Heart rates of our patients (mean 66 beat min^{-1}) were similar to those occurring during natural sleep[11] and the timing of inspiratory onset, relative to R_{-1}, was the same as that found for awake resting and sleeping subjects who exhibit cardioventilatory coupling.[3] Ventilatory frequencies in our patients (mean 20 bpm) were generally a little higher than those found during sleep (15 bpm[11]) and therefore study of the interaction between RSA and coupling in natural sleep would be warranted.

We have demonstrated a close relationship between RSA vagal modulation and heart beat timing during strong cardioventilatory synchronization, where heart beats and inspiration are in perfect synchrony. However, this pattern of coupling occurs to a variable extent; in some anaesthetized patients it makes up the entire data record whereas in others it is absent. We have described previously at least six patterns of coupling.[8] Again the relevance of this interaction between RSA and CVC may depend on the pattern of coupling seen in sleeping subjects and the degree of RSA "optimization" seen with each pattern.

Respiratory sinus arrhythmia diminishes with advancing age whereas phase coupling persists.[2 3] Although this may simply reflect the robustness of the phase coupling mechanism in contrast with the effect of ageing on vagal tone, the persistence of coupling with age may help to maintain the maximum inspiratory acceleration of heart rate in the face of diminishing RSA magnitude. Alternatively, it is possible that coupling may have physiological benefits independent of any effect on optimizing RSA.

In summary, during anaesthesia, cardioventilatory coupling places heart beats at positions relative to inspiratory onset where they are maximally affected by the vagal modulation of respiratory sinus arrhythmia. This interaction between respiratory and cardiac timing strengthens the argument for their having significant and perhaps common physiological roles. Despite its potential importance, cardioventilatory coupling is not incorporated in current models of respiratory sinus arrhythmia and the present trend towards spectral or frequency domain measurement of RSA only serves to mask the timing relationship between heart beats and ventilation at the expense of obtaining frequency information alone. Disordered cardioventilatory timing relationships may have significant implications for critically ill patients, the provision of IPPV and abnormalities of cardiac rate control.

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Cardiovascular effects of 50% nitrous oxide in older adult patients anaesthetized with isoflurane or halothane

M. S. McKinney and J. P. H. Fee

Summary

We have studied the cardiovascular effects of equipotent concentrations of halothane or isoflurane, with or without 50% nitrous oxide in oxygen, in 80 patients, aged 60 yr or more, during 20 min of stable equipotent anaesthesia. Non-invasive measurement techniques were used, with suprasternal Doppler ultrasonography for estimating cardiac output. Both isoflurane and halothane reduced heart rate and systemic arterial pressure. With isoflurane, mean rate decreased from 72 (SD 9.7) to 67 (10.4) beat min^{-1} and with halothane from 76 (10.1) to 65 (9.1) beat min^{-1} ($P<0.05$). Mean diastolic arterial pressure decreased from 81 (11.3) to 58 (17.0) mm Hg with isoflurane and from 86 (14.7) to 70 (13.3) mm Hg with halothane ($P<0.05$). Cardiac index decreased from 3.1 (1.03) to 2.7 (0.71) litre min^{-1} m^{-2} with isoflurane and from 3.1 (0.98) to 2.5 (0.57) litre min^{-1} m^{-2} with halothane ($P<0.05$). Systemic vascular resistance decreased significantly in all groups except those receiving halothane with nitrous oxide. Nitrous oxide resulted in significantly less depression of cardiac index when given with isoflurane than when given with halothane. The mean percentage change in cardiac index during isoflurane anaesthesia without nitrous oxide was 16.7%; with nitrous oxide there was a 0.5% increase. Halothane, in combination with nitrous oxide, resulted in greater depression of cardiac index than isoflurane with nitrous oxide. The mean percentage change with halothane was 20.4% (22.2%); with isoflurane there was a 0.5% (27.1%) increase ($P<0.05$). Hypotension was more pronounced in patients anaesthetized with isoflurane ($n=40$) than those anaesthetized with halothane ($n=40$), irrespective of the presence of nitrous oxide. The mean percentage decrease with isoflurane was 29.7% (21.10%) compared with 16.8% (16.78%) with halothane ($P<0.05$). (*Br. J. Anaesth.* 1998; **80**: 169–173)

Keywords: anaesthetics volatile, halothane; anaesthetics volatile, isoflurane; anaesthetics gases, nitrous oxide; heart, cardiac output; measurement techniques, Doppler ultrasonography; age factors

Nitrous oxide has been shown to cause both deleterious and beneficial changes in arterial pressure and heart rate when given with halothane.[1–3] Martin and colleagues[4] have shown that it improves myocardial contractility during halothane anaesthesia. Previously published work by our group showed that cardiac output was less well maintained in elderly patients compared with their younger counterparts during isoflurane anaesthesia.[5] We attributed this to reduced cardiovascular sensitivity to sympathetic stimulation.

We report on the cardiovascular effects of nitrous oxide when given with halothane or isoflurane in the elderly.

Patients and methods

After obtaining approval from the University Research Ethics Committee and written, informed consent, we studied 80 ASA I or II patients, aged 60 yr or more, within 20% of their predicted lean body mass. Patients were not included if they were receiving cardioactive medication or had a history of cardiovascular disease, had recently received halothane or had a history of malignant hyperpyrexia. Temazepam 10–20 mg orally was given 1 h before the study commenced.

Patients were allocated randomly to one of four groups ($n=20$ in each) to receive isoflurane or halothane at 1 MAC end-tidal concentration in 100% oxygen (1.05% or 0.65%, respectively) or the same agents in a 50% mixture of nitrous oxide in oxygen at 1 MAC (0.55% or 0.35%, respectively). Cardiac output was measured using a Datascope Accucom cardiac output monitor. This device uses the Doppler principle to measure blood velocity in the ascending aorta. Measurements were obtained in duplicate from the suprasternal notch. Baseline measurements of cardiac output, systemic arterial pressure and heart rate were made after a 10-min period of stabilization in the anaesthetic room. Systemic arterial pressure and heart rate were measured by a Datascope Accutorr and the ECG was monitored throughout the study. All the data were collected before surgery commenced.

Anaesthesia was induced with etomidate 0.3 mg kg^{-1} followed by 1-mg increments for initial maintenance. Atracurium 0.5 mg kg^{-1} was given at the same time to facilitate tracheal intubation with a Portex gas sampling tube, performed 90 s after induction. Two minutes after intubation (time 0) the

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Table 1 Patient characteristics, ventilatory and other data for the elderly patients anaesthetized with halothane or isoflurane in 100% oxygen or 50% nitrous oxide in oxygen (mean (SD)). P_I=peak airway inflation pressure. *$P<0.05$

	Halothane		Isoflurane	
	100% Oxygen	50% Nitrous oxide	100% Oxygen	50% Nitrous oxide
Sex (M/W)	11/9	7/13	8/12	8/13
Age (yr)	72 (5.8)	71 (5.8)	70 (7.2)	69 (6.8)
Weight (kg)	69 (14.2)	71 (12.9)	67 (8.0)	67 (12.5)
Height (cm)	167 (8.1)	163 (13.0)	165 (8.6)	167 (9 4)
BSA (m^2)	1.75 (0.206)	1.74 (0.196)	1.70 (0.134)	1.71 (0.189)
Etomidate (mg)	24.7 (5.69)	27.1 (5.35)	23.8 (4.68)	26 1 (5.11)
Atracurium (mg)	36.5 (8.76)	36.3 (6.77)	34.6 (4.30)	34 6 (6.36)
Minute volume (litre)	5.23 (1.219)	5.48 (1.045)	4.83 (0 816)	5.02 (0.858)
Tidal volume (ml)	665 (101.4)	680 (96.5)	648 (88.1)	664 (103.9)
P_I (cm H_2O)	16.1 (3.82)	19.1 (3.24)*	16.1 (3.29)	16.3 (3.41)
Cutaneous weals (*n*)	1	0	0	0

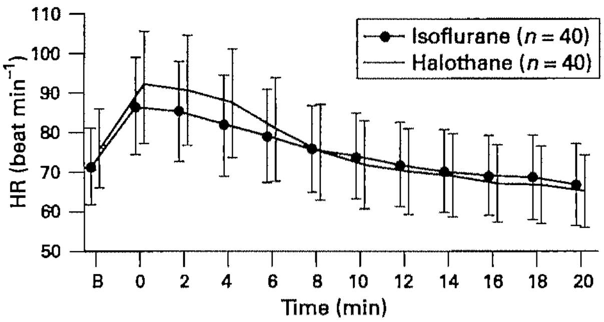

Figure 1 Mean (SD) heart rate (HR) in all subjects receiving isoflurane or halothane.

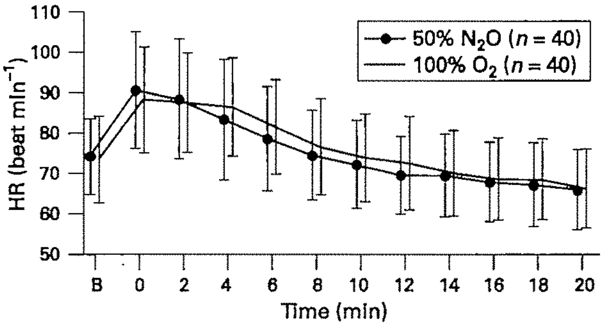

Figure 2 Mean (SD) heart rate (HR) in all subjects receiving either volatile agent and 50% nitrous oxide (N_2O) in oxygen or 100% oxygen (O_2).

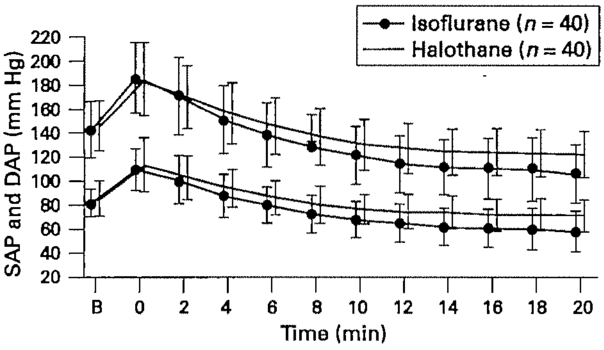

Figure 3 Mean (SD) systolic (SAP) and diastolic (DAP) arterial pressures in patients receiving 1 MAC of isoflurane or halothane.

volatile agent was introduced at an inspired concentration chosen to attain 1 MAC (end-tidal) within 2 min. The lungs were ventilated to an end-tidal carbon dioxide partial pressure of 4.5 kPa. Measurements of arterial pressure, heart rate, cardiac output and volatile agent were made at time 0 and every 2 min for 20 min. During this time the patient remained undisturbed and the inspired volatile agent concentration was adjusted to maintain 1 MAC expired concentration, as measured by a Datex Normac.

Data were collected on-line using a BBC microcomputer which was interfaced with the Accucom and the Normac.[6] The computer collected and stored data on arterial pressure, heart rate and cardiac output, together with other Doppler information (ejection time, signal strength and heart rate). It also sampled intermittently the concentration of volatile agent over a 10-s period from the Normac and calculated peak and trough concentrations of volatile agent. The Normac/computer system was calibrated with a standard gas before each study. Data were stored on diskette for later retrieval. Cardiac index, stroke distance and minute distance were calculated for each measurement using a nomogram-derived estimate for body surface area.

Results were analysed using two- or three-factor repeated measures analysis of variance to give a broad perspective. To improve the power of the factorial design of the study, summary measures were made for each of the measured variables. Two-factor ANOVA was then used to compare the effects of volatile agent or nitrous oxide, or both, using contrast analyses, with the Newman–Keul's test for appropriate individual comparisons. Chi-square and Mann–Whitney *U* tests were applied to non-parametric data. $P<0.05$ was considered statistically significant.

Results

Table 1 shows patient characteristics, ventilation and drug doses for the four study groups.

Over the duration of the study, isoflurane (n=40) had less of an effect on heart rate than halothane (n=40) (fig. 1) and the addition of nitrous oxide did not alter the changes in heart rate (n=40) (fig. 2).

Halothane (n=40) caused a smaller decrease in both systolic and diastolic arterial pressures than isoflurane ($P<0.05$) (fig. 3) but these effects were reduced by the addition of nitrous oxide (n=40) ($P<0.05$) (fig. 4).

Cardiac index decreased significantly over the study in all groups (n=80) (fig. 5) and was affected similarly by the two agents (table 2). The addition of nitrous oxide produced different effects on cardiac index depending on the volatile agent: with isoflurane it was better maintained ($P<0.05$) (n=20) but with halothane the depression was accentuated ($P<0.05$) (n=20) (fig. 6).

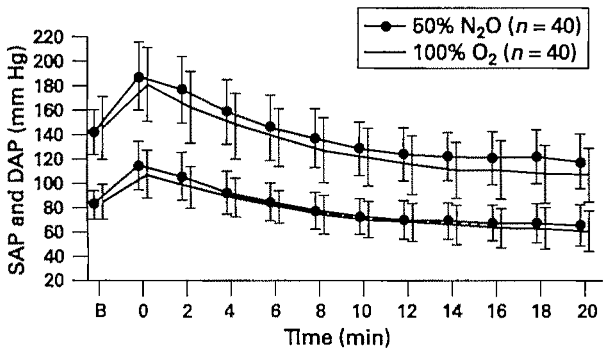

Figure 4 Mean (SD) systolic (SAP) and diastolic (DAP) arterial pressures in patients receiving either volatile agent and 50% nitrous oxide in oxygen or 100% oxygen.

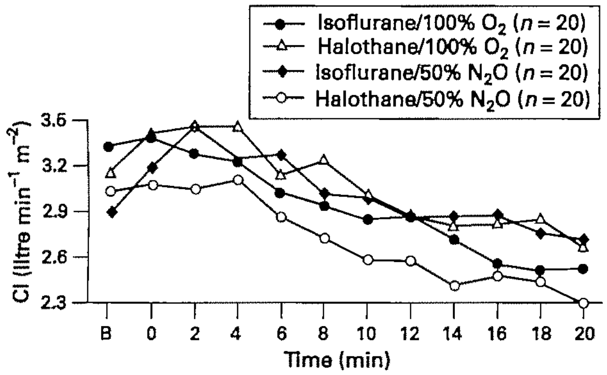

Figure 5 Mean (SD) cardiac index (CI) in all four groups.

Table 2 Mean (SD) cardiac index values at baseline and after 20 min of 1 MAC of anaesthesia. Summary data are presented under each category. For example, in the case of isoflurane, the mean cardiac index is calculated from the pooled isoflurane—nitrous oxide (N_2O) and isoflurane—oxygen (O_2) data

	Baseline	20 min
All isoflurane cases	3.1 (1.03)	2.7 (0.71)
All halothane cases	3.1 (0.98)	2.5 (0.57)
All 50% N_2O—O_2 cases	3.0 (0.80)	2.5 (0.60)
All 100% O_2 cases	3.2 (1.16)	2.7 (0.70)

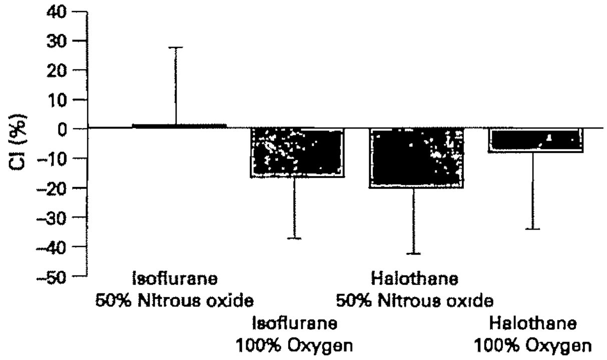

Figure 6 Mean (SD) percentage change in cardiac index (CI) from baseline values in the four groups.

Systemic vascular resistance was reduced to a greater extent by isoflurane than halothane (n=40) (P<0.05) (fig. 7). There was little change when nitrous oxide was added to either agent (n=40) (P> 0.05) (fig. 8).

Discussion

Ventilation to an end-tidal carbon dioxide value of 4.5 kPa was based on previous work[7] which demonstrated that this value resulted in normocapnia in this age group of patients. Indeed, arterial blood samples showed that mean arterial $P\text{CO}_2$ was 4.9 kPa.

Atracurium was chosen because of its minimal effect on the cardiovascular system. Other neuromuscular blocking agents have been associated with vagal reactions and altered pharmacokinetics in the elderly.

Most studies on the cardiovascular effects of nitrous oxide alone would suggest that it exhibits a sympathomimetic action[8 9] and these effects have also been demonstrated when nitrous oxide is used in conjunction with other anaesthetic agents, with an increased systemic vascular resistance being the most consistent finding.[4 10 11]

Reports on the effect of nitrous oxide in combination with volatile anaesthetic agents on heart rate have been inconsistent.[11–13] In the older adult, isoflurane in oxygen was associated with a decrease in heart rate[5] and the addition of nitrous oxide (with equal anaesthetic potency) has now been shown to increase this effect. Halothane in oxygen was also associated with a reduced heart rate but nitrous oxide did not change this effect. These findings, attributed to the limited responsiveness of the aged cardiovascular system to sympathomimetic effects,[14–19] may explain the absence of an increase in heart rate in this study.

It has been demonstrated previously that nitrous oxide reduces the decline in arterial pressure associated with isoflurane[12 20] and halothane[21 22] in healthy young adults, a finding corroborated by these results. The use of 100% oxygen in the control group may itself have contributed to some cardiovascular changes, although oxygen alone has been shown to increase arterial pressure and systemic vascular resistance.[23]

Systemic vascular resistance was increased by the addition of nitrous oxide to halothane but was reduced similarly in both groups receiving isoflurane anaesthesia. As a sole agent or in conjunction with halothane, nitrous oxide has been shown to exert a peripheral vasoconstricting effect in healthy adults and animals.[3 10 11 24] However, these effects were not replicated during isoflurane anaesthesia; indeed Dolan and colleagues[20] indicated that systemic vascular resistance was higher in the absence of nitrous oxide, although they did not compensate for altered anaesthetic potency.

Isoflurane, halothane and nitrous oxide exhibit dose-dependent myocardial depression by interacting with Ca^{2+} effects in the myocyte,[25–27] although the exact mechanisms may differ between halothane and isoflurane.[28–30] Reducing the concentration of the volatile agent by adding a less potent myocardial depressant drug (nitrous oxide)[26] should reduce depression of cardiac function, but we found that this occurred only with isoflurane. Lawson, Frazer and Lynch[27] found that nitrous oxide, in common with halothane, reduced Ca^{2+} release from the sarcoplasmic reticulum of the myocyte but that the effects of isoflurane were of a different character. However, they found that the addition of nitrous oxide to either halothane or isoflurane caused simple additive depression of myocardial function with both agents. There is evidence that uptake of Ca^{2+} by sarcoplasmic reticulum of aged myocytes is deficient[31] and this

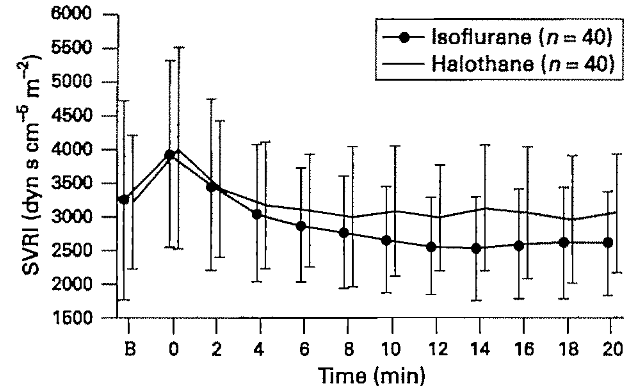

Figure 7 Mean (SD) systemic vascular resistance index (SVRI) in patients receiving 1 MAC of isoflurane or halothane.

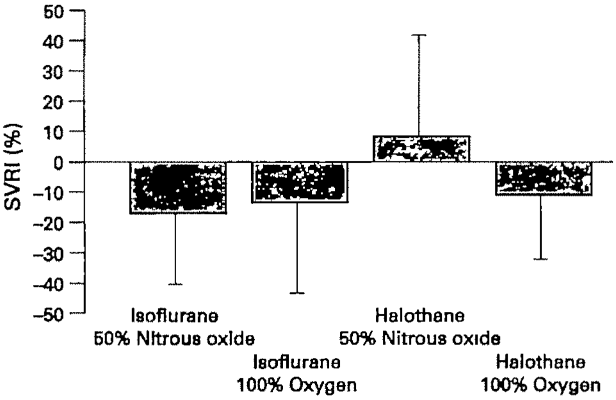

Figure 8 Mean (SD) percentage change in systemic vascular resistance index (SVRI) in the four groups.

would result in a lower Ca^{2+} content of the sarcoplasmic reticulum.[32] Thus the combined effects of halothane and nitrous oxide on release of Ca^{2+} from this organelle may be more potent in the older heart. Certainly, nitrous oxide produced a marked decrease in stroke volume during halothane anaesthesia whereas a significant increase was seen with isoflurane.

Cardiovascular changes are modified in the intact animal by autonomic corrective reflexes. Together with halothane, isoflurane, and the effects of ageing,[33 34] nitrous oxide has been shown to reduce baroreflex function.[3] However, Duke and Trosky[2] suggested that baroreflex depression at equipotent anaesthetic concentrations with halothane was less when nitrous oxide formed part of the technique. Although arterial pressure was still decreased when nitrous oxide was used, the corrective heart rate response was not seen in this study. In fact, there was further slowing of the heart during isoflurane anaesthesia. This may suggest that the baroreflex is reset at a lower level and that the slightly higher arterial pressure in the presence of nitrous oxide results in reflex slowing of the heart.

The presence of nitrous oxide in the anaesthetic gas mixture should result in a faster uptake of volatile agent as a result of the second gas effect.[35 36] This would shorten the onset time of the volatile agent and may be partly the reason for the greater depression when nitrous oxide is added to halothane.

In summary, 1 MAC of isoflurane anaesthesia with 50% nitrous oxide in older adult patients resulted in less depression of systemic arterial pressure and cardiac output than 1 MAC (equipotent) of isoflurane alone; there was, however, greater depression of heart rate. Systemic vascular resistance was unaffected. Nitrous oxide with halothane resulted in a greater decrease in cardiac output, increased systemic vascular resistance and no alteration in heart rate. This suggests that, in terms of cardiovascular responses, nitrous oxide supplementation may be beneficial during isoflurane, and detrimental during halothane anaesthesia in older age groups.

Acknowledgements

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British Journal of Anaesthesia 1998; **80**: 174–182

Influence of 0.1 minimum alveolar concentration of sevoflurane, desflurane and isoflurane on dynamic ventilatory response to hypercapnia in humans

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Summary

To assess the effects and site of action of a subanaesthetic concentration of isoflurane, desflurane and sevoflurane (0.1 minimum alveolar concentration (MAC)) on respiratory control, we measured the ventilatory response to square wave changes in PE'_{CO_2} against a background of normoxia. Using the computer steered "end-tidal forcing system", 2 min of steady state ventilation were followed by a step increase in PE'_{CO_2} (1–1.5 kPa). This level was maintained for 8 min, followed by a step decrease to the original value for another 8 min. Each hypercapnic response was separated into a fast, peripheral component and a slow, central component, characterized by a time constant, carbon dioxide sensitivity, time delay and off-set. We studied 25 healthy volunteers; they performed 2–3 studies without and 2–3 studies during inhalation of the anaesthetic agent. Level of sedation was scored using a subjective seven-point scale from 0 (= alert and awake) to 6 (unrousable). In the isoflurane (16 subjects, 33 control, 37 drug studies) and sevoflurane (15 subjects, 40 control, 41 drug studies) studies, peripheral carbon dioxide sensitivity was reduced by approximately 45% and approximately 27% (ANOVA, $P < 0.05$ *vs* control), respectively, without affecting central carbon dioxide sensitivity or apnoeic threshold. In the desflurane study (16 subjects, 36 control, 37 drug studies), no significant effect was observed for any of the variables measured. A significant relation was observed between sedation score and change from control in central carbon dioxide sensitivities in the isoflurane and desflurane studies and in the change in the ratio peripheral carbon dioxide sensitivity over total carbon dioxide sensitivity in the sevoflurane studies. At the highest level of sedation observed (score 3–arousal state comparable with "light sleep"–in three subjects) these latter variables differed significantly from those in the other observed sedation levels (scores 1 and 2–a state of drowsiness). We conclude that 0.1 MAC of isoflurane and sevoflurane depressed the peripheral chemoreflex loop, without affecting the central chemoreflex loop. Desflurane at the same MAC showed no effect on peripheral and central carbon dioxide sensitivity. When the level of sedation was considered, our data suggested that at levels of sedation comparable with sleep, a depressive effect of all three anaesthetics was observed on the central chemoreflex loop. (*Br. J. Anaesth.* 1998; **80**: 174–182)

Keywords: anaesthetics volatile, desflurane; anaesthetics volatile, isoflurane; anaesthetics volatile, sevoflurane; ventilation, hypoxic response; hypoxaemia

Sevoflurane and desflurane are two new inhalation anaesthetics. Earlier studies from our laboratory showed that in healthy volunteers, desflurane at 0.1 minimal alveolar concentration (MAC) did not affect the ventilatory response to normocapnic hypoxia but decreased significantly the response to asphyxia (hypercapnic hypoxia).[1] Sevoflurane at 0.1 MAC caused a reduction in the hypoxic response by approximately 30%.[2] Similar MAC fractions of isoflurane and halothane produced a more marked decrease in the hypoxic response (50% or more) in an equivalent group of healthy subjects.[3 4] Results of studies on the influence of 0.1 MAC of halothane and isoflurane on the ventilatory response to inhaled carbon dioxide were in agreement with the results of the hypoxic studies.[3 4] Moreover, carbon dioxide studies revealed a selective depressant effect of 0.1 MAC of halothane and isoflurane on the peripheral chemoreflex loop. None of the anaesthetics tested showed a significant effect on carbon dioxide sensitivity of the central chemoreceptors.

In order to study the influence of 0.1 MAC of desflurane and sevoflurane on the carbon dioxide related output of the peripheral and central chemoreflex loops, we determined ventilatory responses to square-wave changes in end-tidal carbon dioxide tension (PE'_{CO_2}) against a background of normoxia. The ventilatory responses, measured on a breath-by-breath basis were then partitioned into a fast, peripheral and a slow, central component, using a two-compartment model.[5 6]

Subjects and methods

We studied 25 healthy volunteers (12 women, 13 men, aged 22–37 yr), with no history of smoking, drug or alcohol abuse. The study was approved by the Leiden

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University Committee on Medical Ethics and informed consent was obtained before the study. Subjects were unfamiliar with respiratory physiology but received information on the nature of the study. All had participated in several studies on respiratory physiology in our laboratory. Therefore, a test session was not required. Subjects were asked to refrain from stimulants and depressants for at least 12 h before the study.

During the study, subjects were in a semi-recumbent position (135° between lower extremities and thorax). Soft music was played and subjects were instructed to keep their eyes closed throughout the studies. An oronasal mask (Vital Signs, USA) was fitted before the experiment started. Airway gas flow was measured with a pneumotachograph (Fleisch, Switzerland) connected to a differential pressure transducer (model 270, Hewlett Packard, USA) and integrated electronically to yield a volume signal. This signal was calibrated with a motor-driven piston pump. The pneumotachograph was connected to a T-piece. One arm of the T-piece received a gas mixture with a flow of 50 litre min^{-1} from a gas mixing system that consisted of three mass flow controllers (type F201, Bronkhorst High Tec, The Netherlands) with which the flow of oxygen, carbon dioxide and nitrogen could be set individually at a desired level. A PDP 11/23 microcomputer (Digital Equipment Corporation, Maynard, USA) provided control signals to the mass flow controllers, so that the composition of the inspiratory gas mixture could be adjusted to force the end-tidal carbon dioxide and oxygen partial pressures to follow a specific pattern in time. When appropriate, part of the nitrogen (5 litre min^{-1}) was bypassed through the isoflurane, sevoflurane or desflurane vaporizer. During the initial part of the study, the vaporizer was kept in the "off" position. Inspiratory and expiratory concentrations of oxygen and carbon dioxide were measured with a gas monitor (Datex Multicap, Finland) by paramagnetic and infrared analysis, respectively. The gas monitor was calibrated with gas mixtures of known concentrations. The concentrations of isoflurane, desflurane and sevoflurane were measured at the mouth with a Datex Capnomac Ultima. Inspiratory minute ventilation ($\dot{V}\mathrm{I}$), and end-tidal concentrations of oxygen and carbon dioxide ($P\mathrm{E}'_{\mathrm{O_2}}$ and $P\mathrm{E}'_{\mathrm{CO_2}}$, respectively) were calculated and stored on a breath-by-breath basis.

STUDY DESIGN

We used a computer steered "end-tidal forcing system" to obtain stepwise increases and decreases in $P\mathrm{E}'_{\mathrm{CO_2}}$ while maintaining $P\mathrm{E}'_{\mathrm{O_2}}$ at a normoxic level ($P\mathrm{E}'_{\mathrm{O_2}}$ =14.5 kPa). After arrival in the laboratory, subjects rested for at least 30 min. Each hypercapnic study started with a period of "steady-state" ventilation of approximately 10 min during which $P\mathrm{E}'_{\mathrm{CO_2}}$ was held at 0.2–0.3 kPa above resting. The reason for this increase was to allow the end-tidal forcing system adequately to control $P\mathrm{E}'_{\mathrm{CO_2}}$ by manipulation of the inspired $P\mathrm{CO_2}$. Subsequently, $P\mathrm{E}'_{\mathrm{CO_2}}$ was increased by 1–1.5 kPa within 3–5 breaths, maintained constant for approximately 8 min and then returned, in a single step, to the original value and maintained for another 8 min.

Each subject performed 2–3 studies without and 2–3 studies during inhalation of the anaesthetic agent. Control studies always preceded drug studies. Before we started a drug experiment we allowed an equilibration period of 20 min for isoflurane and 15 min for sevoflurane and desflurane after the appropriate end-tidal concentration had been reached. The target end-tidal concentrations used were 0.125%, 0.72% and 0.22% (approximately 0.1 MAC) for isoflurane, desflurane and sevoflurane, respectively. Throughout the studies, end-tidal concentrations were maintained at target levels by manipulation of the vaporizer by one of the investigators (M. vd E., E. S. or A. D.).

Sixteen subjects participated in the isoflurane and desflurane studies and 15 in the sevoflurane study. Seven subjects participated in all three studies. A single anaesthetic was tested on a particular morning session. Sessions were at least 2 weeks apart. The results of the isoflurane studies of eight subjects have been published previously.[4]

DATA ANALYSIS

The steady-state relation of $\dot{V}\mathrm{I}$ TO $P\mathrm{E}'_{\mathrm{CO_2}}$ at constant $P\mathrm{E}'_{\mathrm{O_2}}$ in humans is described by:

$$\dot{V}\mathrm{I} = (G_{\mathrm{P}} + G_{\mathrm{C}})\ (P\mathrm{E}'_{\mathrm{CO_2}} - B) \qquad (1)$$

where G_{P} = carbon dioxide sensitivity of the peripheral chemoreflex loop; G_{C} = carbon dioxide sensitivity of the central chemoreflex loop; and B = apnoeic threshold or extrapolated $P\mathrm{E}'_{\mathrm{CO_2}}$ of the steady-state ventilatory response to carbon dioxide at zero $\dot{V}\mathrm{I}$. The sum of G_{P} and G_{C} is total carbon dioxide sensitivity (G_{TOT}).

For analysis of the dynamic response of ventilation, we used a two-compartment model[5 6]:

$$\tau_{\mathrm{P}}\ \mathrm{d}/\mathrm{d}t\ \dot{V}_{\mathrm{P}}\ (t) = G_{\mathrm{P}}\ (P\mathrm{E}'_{\mathrm{CO_2}}\ (t - D_{\mathrm{P}}) - B) - \dot{V}_{\mathrm{P}}\ (t) \qquad (2)$$

$$\tau_{\mathrm{C}}\ \mathrm{d}/\mathrm{d}t\ \dot{V}_{\mathrm{C}}\ (t) = G_{\mathrm{C}}\ (P\mathrm{E}'_{\mathrm{CO_2}}\ (t - D_{\mathrm{C}}) - B) - \dot{V}_{\mathrm{C}}\ (t) \qquad (3)$$

where τ_{P} and τ_{C} = time constants of the peripheral and central chemoreflex loops, respectively; $\dot{V}_{\mathrm{P}}\ (t)$ and $\dot{V}_{\mathrm{C}}\ (t)$ = outputs of the peripheral and central chemoreflex loops, respectively; $P\mathrm{E}'_{\mathrm{CO_2}}\ (t - D_{\mathrm{P}})$ = stimulus to peripheral chemoreflex loop delayed by the peripheral transport delay time (D_{P}); and $P\mathrm{E}'_{\mathrm{CO_2}}\ (t - D_{\mathrm{C}})$ = stimulus of the central chemoreflex loop delayed by the central transport delay time (D_{C}). The time delay represents the transit time for the $P\mathrm{E}'_{\mathrm{CO_2}}$ stimulus to reach the chemoreceptors.

To model τ_{C} of the ventilatory on-transient (τ_{ON}) to be different from that of the off-transient (τ_{OFF}), τ_{C} is written as:

$$\tau_{\mathrm{C}} = \tau_{\mathrm{ON}}\ x + (1 - x)\ \tau_{\mathrm{OFF}} \qquad (4)$$

where $x = 1$ when $P\mathrm{E}'_{\mathrm{CO_2}}$ is high and $x = 0$ when $P\mathrm{E}'_{\mathrm{CO_2}}$ is low.

In most experiments a small drift in ventilation was present. We therefore included a drift term (Ct) in our model. The total ventilatory response $\dot{V}\mathrm{I}(t)$ is made up of the contributions of the central and peripheral chemoreflex loops and Ct:

$$\dot{V}\mathrm{I}(t) = \dot{V}_{\mathrm{P}}(t) + \dot{V}_{\mathrm{C}}(t) + Ct \qquad (5)$$

The parameters of the model were estimated by fitting the model to the breath-by-breath data with a least-squares method. To obtain optimal time delays a "grid search" was applied. All combinations of D_{P} and D_{C}, with increments of 1 s and with $D_{\mathrm{P}} \leqslant D_{\mathrm{C}}$ were tried until a minimum in the residual sum of squares was found. The minimum time delay was chosen arbitrarily to be 1 s, and τ_{P} was constrained to be at least 0.3 s.

Table 1 Leiden observer's assessment of alertness/sedation (LOAA/S) scale

0 = Normal alertness, eyes closed and opened on command
1 = Drowsy with open eyes, closed and opened on demand
2 = Drowsy with closed eyes, opened in response to a light auditory stimulus
3 = Eyes closed, opened in response to rubbing the shoulder or a loud auditory stimulus
4 = Closed eyes, eyes opened only briefly in response to touching the subject
5 = Closed eyes, unrousable by touching the subject, aroused by a painful stimulus
6 = Unrousable by a painful stimulus

SCORING FOR SEDATION AND EXCLUSION CRITERIA

At the start and end of each hypercapnic study, we recorded the central nervous system arousal state by a subjective six-point observer's assessment of alertness/sedation (LOAA/S) scale (table 1). Data were discarded when the LOAA/S score was not 0 in the control studies, irregular breathing, coughing or an apparent change in the arousal state (for example as observed by restlessness) occurred in any of the studies.

STATISTICAL ANALYSIS

For each volatile agent, we determined the significance of differences between the control and drug studies by two-way analysis of variance (ANOVA) on parameters G_P, G_C, G_P/G_{TOT} (ratio) and B using a fixed model. To obtain information on the relationship between sedation score and the difference between drug and control parameters (Δ) we performed a linear regression analysis of ΔG_P, ΔG_C and $\Delta G_P/G_{TOT}$ (Δratio) on sedation score. Further, we determined for each anaesthetic the significance of differences between sedation scores by ANOVA on ΔG_P, ΔG_C and Δratio with *post hoc* multiple comparisons using Newman–Keuls test. Probability levels <0.05 were considered significant. All values are mean (SD), unless otherwise stated.

Results

All subjects completed the study without side effects. A total of 235 ventilation–$P\text{E}'_{CO_2}$ responses were obtained. Eleven studies were discarded because of irregular breathing (four control and seven drug studies, of which isoflurane two, desflurane two and sevoflurane three).

ISOFLURANE STUDIES

Thirty-three control and 37 isoflurane studies were included in the analysis. End-tidal isoflurane concentrations were 0.13 (0.04)% in the drug studies. The LOAA/S scores were 0 in the control studies for all subjects. In the isoflurane studies, scores were 1 in six, 2 in seven and 3 in three subjects. Isoflurane at 0.1 MAC caused peripheral carbon dioxide sensitivity to decrease by 45% ($P = 0.003$), without affecting central carbon dioxide sensitivity or apnoeic threshold (table 2). These changes caused the ratio of peripheral carbon dioxide sensitivity to total carbon dioxide sensitivity ($G_P/(G_P + G_C)$) to decrease by 35% (P=0.01).

SEVOFLURANE STUDIES

Forty control and 41 sevoflurane studies were included in the analysis. End-tidal sevoflurane concentrations were 0.22 (0.04)% in the drug studies. The LOAA/S scores were 0 in the control studies for all subjects. In the sevoflurane studies, scores were 1 in six, 2 in six and 3 in three subjects. During sevoflurane inhalation, peripheral carbon dioxide sensitivity decreased by 27% (P=0.02). Central carbon dioxide sensitivity, ratio and apnoeic threshold were not affected by 0.1 MAC of sevoflurane. The typical fits to the data of two studies of one subject are shown in figure 1.

DESFLURANE STUDIES

Thirty-six control and 37 desflurane studies were included in the analysis. End-tidal desflurane concentrations were 0.70 (0.04)% in the drug studies. The LOAA/S scores were 0 in the control studies for all subjects. In the desflurane studies, scores were 1 in six, 2 in seven and 3 in three subjects. The model fits of a control and desflurane experiment of a subject are shown in figure 1. They indicate no effect on the peripheral or central chemoreflex loop. None of the estimated parameters differed significantly between control and desflurane studies (table 2).

In figure 2, scatter diagrams for G_P, G_C and ratio are given for all three anaesthetics.

INFLUENCE OF LEVEL OF SEDATION

Regression analysis revealed a significant relation between LOAA/S score and the difference in central carbon dioxide sensitivity between drug and control (ΔG_C) in the isoflurane and desflurane studies. The

Table 2 Mean (SD) [95% confidence intervals] values of the estimated parameters. G_C = carbon dioxide sensitivity of the central chemoreflex loop; G_P = carbon dioxide sensitivity of the peripheral chemoreflex loop; B = apnoeic threshold. *16 subjects; †15 subjects

	Isoflurane*			Sevoflurane†			Desflurane*		
	Control	Drug	ANOVA	Control	Drug	ANOVA	Control	Drug	ANOVA
Number of runs	33	37		40	41		36	37	
G_C (litre min^{-1} kPa^{-1})	8.9 (3.2) [7.2–10.7]	8.0 (3.6) [6.1–10.0]	ns	10.4 (5.8) [7.3–13.7]	9.9 (5.8) [6.7–13.1]	ns	10.4 (4.8) [7.9–12.9]	9.0 (4.8) [6.5–11.7]	ns
G_P (litre min^{-1} kPa^{-1})	4.2 (1.6) [3.2–5.1]	2.3 (1.6) [1.6–3.1]	P=0.003	3.7 (1.5) [2.8–4.7]	2.7 (1.9) [1.7–3.7]	P=0.02	3.7 (1.8) [2.8–4.6]	3.2 (1.2) [2.6–3.8]	ns
$G_P/(G_C+G_P)$	0.34 (0.12) [0.14–0.29]	0.22 (0.12) [0.16–0.28]	P=0.01 0.01	0.28 (0.12) [0.22–0.34]	0.22 (0.15) [0.15–0.30]	ns	0.27 (0.17) [0.19–0.35]	0.28 (0.10) [0.23–0.31]	ns
B (kPa)	4.4 (0.8) [4.0–4.8]	4.3 (1.0) [3.7–4.9]	ns	4.6 (0.8) [4.2–5.0]	4.4 (1.1) [3.8–5.0]	ns	4.5 (0.8) [4.1–4.9]	4.2 (0.8) [3.8–4.6]	ns

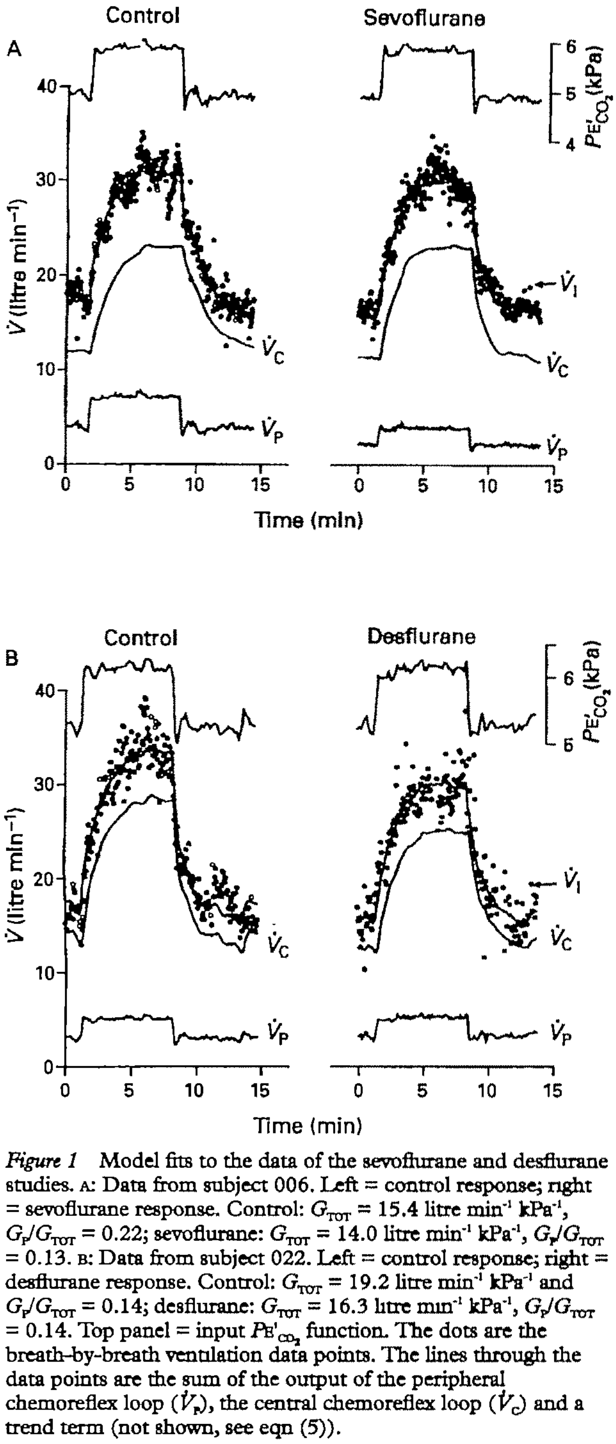

Figure 1 Model fits to the data of the sevoflurane and desflurane studies. A: Data from subject 006. Left = control response; right = sevoflurane response. Control: G_{TOT} = 15.4 litre min^{-1} kPa^{-1}, G_P/G_{TOT} = 0.22; sevoflurane: G_{TOT} = 14.0 litre min^{-1} kPa^{-1}, G_P/G_{TOT} = 0.13. B: Data from subject 022. Left = control response; right = desflurane response. Control: G_{TOT} = 19.2 litre min^{-1} kPa^{-1} and G_P/G_{TOT} = 0.14; desflurane: G_{TOT} = 16.3 litre min^{-1} kPa^{-1}, G_P/G_{TOT} = 0.14. Top panel = input $P\text{E}'_{CO_2}$ function. The dots are the breath-by-breath ventilation data points. The lines through the data points are the sum of the output of the peripheral chemoreflex loop ($\dot{V}_P$), the central chemoreflex loop ($\dot{V}_C$) and a trend term (not shown, see eqn (5)).

value of ΔG_C was smallest in the group with LOAA/S score 3 ($P < 0.05$; see figure 3). In the sevoflurane studies, we observed a significant relation between Δratio and LOAA/S score with Δratio greatest in the group with LOAA/S score 3 ($P < 0.05$; see figure 3). It is of interest to note that subjects with an LOAA/S score of 3 were three females that had participated in all three anaesthetic studies. Their LOAA/S scores were similar in the anaesthetic studies. Exclusion of their data from the analysis would not have affected the conclusion drawn from this study considerably (see fig. 4).

Discussion

Knill and colleagues were the first to study the effects of low concentrations of inhalation anaesthetics on the regulation of breathing in humans.[7–10] In the late 1970s and early 1980s, they tested the effects of halothane, enflurane and isoflurane using several imposed chemical stimuli. Their studies led to the, still generally accepted, conclusion that inhalation anaesthetics selectively impair all responses mediated by the peripheral chemoreceptors at subanaesthetic concentrations (0.05–0.1 MAC).

In order to study the different components of the ventilatory control system, Knill and colleagues used several tests. Using a carbon dioxide rebreathing technique to study the "central" ventilatory response to inhaled carbon dioxide, they observed no depression with 0.1 MAC halothane and isoflurane but approximately 25% depression with 0.1 MAC of enflurane.[7–9] To selectively study the peripheral chemoreflex loop they determined the ventilatory response to a gradual decrease in $P\text{E}'_{O_2}$ over 8–10 min (a so-called "ramp hypoxic step") and to moderate isocapnic metabolic acidosis.[7–10] Hypoxic studies showed a 60% reduction in the ventilatory response with all three anaesthetics at 0.1 MAC; the response to metabolic acidosis was reduced by 60% with 0.1 MAC of halothane. These studies indicated that at least halothane and isoflurane, at 0.1 MAC, affect ventilatory control selectively via an effect on the peripheral chemoreflex loop without an effect on the central chemoreflex loop or pathways common to both loops.

Some of the techniques used by Knill and colleagues have recently come under criticism. The carbon dioxide rebreathing technique, although simple in use, leads to results that are often difficult to interpret, as factors other than those under study determine outcome (such as initial concentration of carbon dioxide in the bag and arterial or end-tidal $P\text{CO}_2$; see Dahan and colleagues[11] and Berkenbosch and colleagues[12] for an analysis of the rebreathing technique). In this respect it is interesting that the results from rebreathing tests in the studies of Knill and colleagues were not uniform for all three anaesthetics. Temp, Henson and Ward demonstrated that the ramp hypoxic test does not allow adequate time for full expression of the hypoxic response from the peripheral chemoreceptors.[13] Tests that allow a more rapid decrease in $P\text{E}'_{O_2}$ (step hypoxic test) are better suited for this purpose and, furthermore, enable the description of the depressant effects of hypoxia.

Despite the important results of the studies of Knill's group it took his personal request and approximately 20 yr before researchers from five independent laboratories investigated the influences of volatile agents on the ventilatory response to imposed chemical stimuli in humans.[14] The availability of hypoxic and hypercapnic tests that give results with less problems in interpretation (compared with the carbon dioxide rebreathing test and the ramp hypoxic test) is probably one of the main reasons. In table 3, data of hypoxic studies from the recent literature are summarized. The results of three institutions indicate an appreciable depressant effect of halothane, enflurane, isoflurane and sevoflurane on the acute hypoxic response to an isocapnic step decrease in $P\text{E}'_{O_2}$.[2–4 15–21] With respect to isoflurane, the results from UCLA and the Karolinska Institute indicate little or only a modest effect on the hypoxic response.[13 22–24 26] To explain these differences we have to take into account the significant differences in the

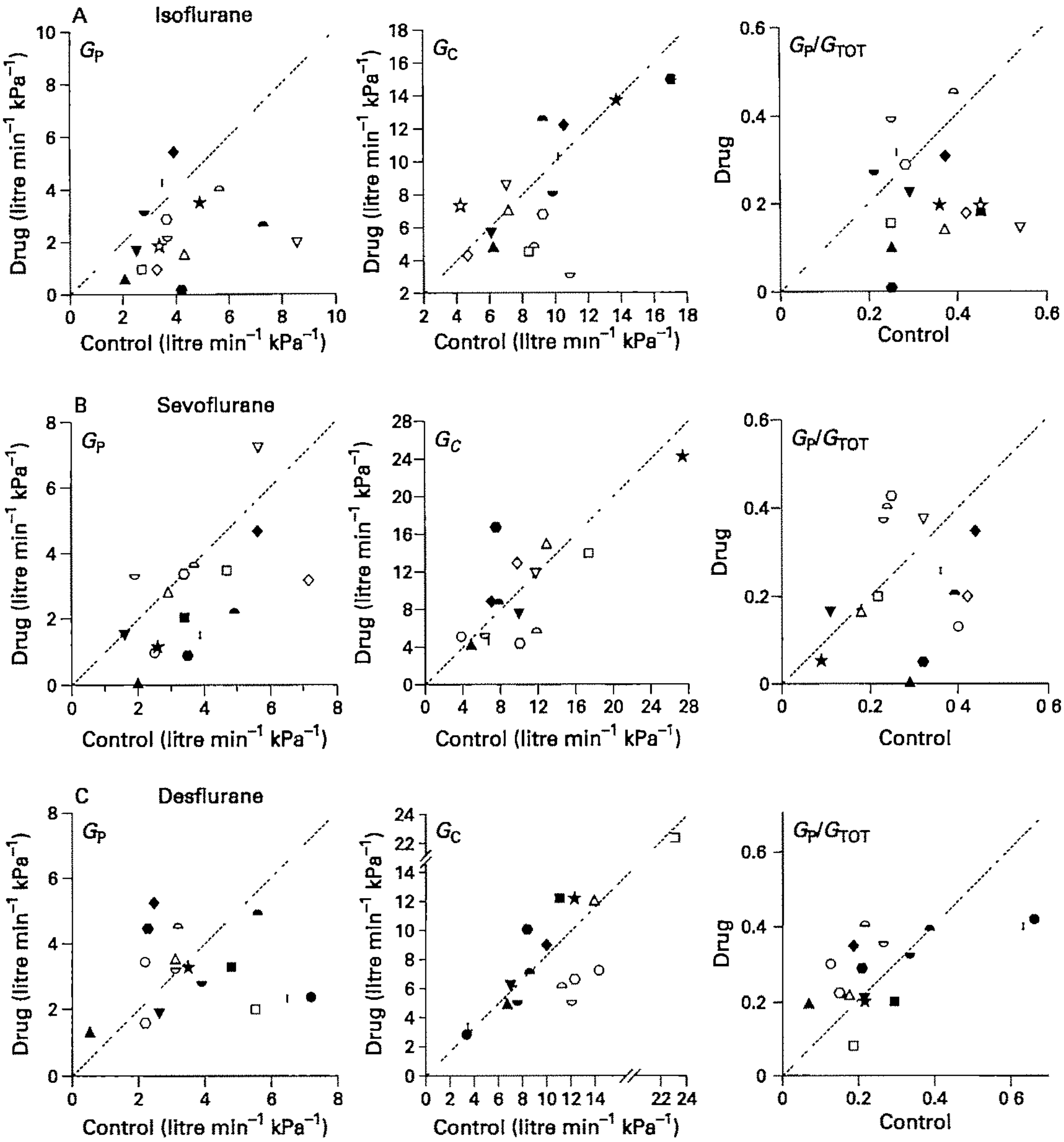

Figure 2 Scatter diagrams of the mean ventilatory carbon dioxide sensitivities of the peripheral (G_P) and central (G_C) chemoreflex loops and the ratio G_P/G_{TOT} ($G_{TOT} = G_P + G_C$). A: Isoflurane study. Each subject has similar symbols in the three diagrams. B = Sevoflurane study; C = desflurane study.

design of the studies. For example, in contrast with the hypoxic studies from the Karolinska Institute and Edinburgh,[16,20,22–25] all those performed in Oxford, UCLA and Leiden had an increased baseline $P\text{E}'_{CO_2}$ of 0.1–0.3 kPa.[3,4,13,15,17–19,21,26] Some of the hypoxic studies from the Karolinska Institute and Edinburgh were not performed under isocapnic conditions or allowed differences in $P\text{E}'_{CO_2}$ between control and drug studies.[16,22–25] One study from Oxford and both from UCLA had an approach to prevent subjects from falling "asleep".[13,18,26] However, we believe that these differences only partly explain the discrepancies in study outcomes.

In comparison with hypoxic studies, studies that investigate the influence of anaesthetics on the ventilatory response to inhaled carbon dioxide are scarce. Previously, we compared the effects of 0.1 MAC of halothane and isoflurane, and observed a 20–25% reduction in steady-state normoxic ventilatory carbon dioxide sensitivity.[3,4] Analysis of the dynamic ventilatory response with the same two-compartment model used in this study revealed that this could be attributed to an effect within the peripheral chemoreflex loop (G_P reduced by approximately 50%) These results are in agreement with those of the hypoxic studies obtained from three of the five institutions (table 3). In contrast, a hypercapnic study from the Karolinska Institute showed no effect of 0.2% end-tidal isoflurane on carbon dioxide sensitivity (anaesthetic response = 0.96 of control response (ns)).[24]

EQUI-MAC-FRACTION DATA

In this study, isoflurane and sevoflurane at 0.1 MAC significantly reduced peripheral carbon dioxide sensitivity without affecting central carbon dioxide sensitivity and the apnoeic threshold. This indicates a selective depressant effect of both anaesthetics on the peripheral chemoreflex loop. These results are in agreement with our hypoxic studies in which we observed a reduction in the acute hypoxic ventilatory response by approximately the same magnitude at 0.1 MAC.[2,4] Desflurane did not influence the ventilatory response to carbon dioxide significantly. With respect to G_P, a decrease was observed in nine

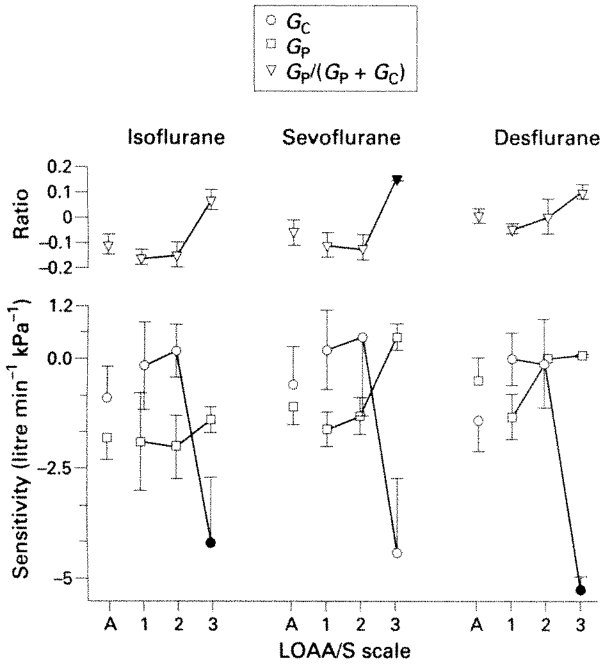

Figure 3 Influence of Leiden observer's assessment of alertness/sedation (LOAA/S) scale on the change from control (Δ) in central carbon dioxide sensitivity (G_C), peripheral carbon dioxide sensitivity (G_P) and ratio ($G_P/(G_P + G_C)$). Regression analysis revealed a significant relation between ΔG_C and LOAA/S in the isoflurane and desflurane studies, and between Δratio and LOAA/S in the sevoflurane studies. The closed data points denote LOAA/S scores significantly different from other scores ($P < 0.05$, ANOVA). A = All scores combined. Values are mean (SEM).

of 16 subjects (there was a trend towards a reduction by approximately 15%). In a previous study we were unable to demonstrate an effect of 0.1 MAC of desflurane on the hypoxic response at normocapnia.[1] However, in that study the ventilatory response to asphyxia was reduced by approximately 30%. This indicates that the peripheral chemoreflex loop does not remain completely unaffected by 0.1 MAC of desflurane. A type II error, therefore, may not be excluded in our current study. The reason for the difference between desflurane and the other two anaesthetics remains unclear. At higher concentrations, desflurane is known to increase sympathetic outflow and irritate the airways.[27 28] We did not observe any signs related to airway irritation or sympathetic activation (for example coughing, breath-holding, sneezing or tachycardia). However, subclinical activation of the sympathetic system and systemic release of catecholamines during hypercapnia and hypoxia may be a possible explanation for the absence of depression of the normoxic ventilatory response to carbon dioxide. It is of interest to note that nitrous oxide, another sympathomimetic agent, at 0.2 MAC influences the ventilatory responses to hypoxia and hypercapnia in a manner similar to desflurane.[29]

At this point, we have to keep in mind that when considering the LOAA/S scores as a measure of the CNS arousal state of individual subjects (equi-sedative data) the above stated conclusions (drawn from equi-MAC-fraction data) need some modification (see below).

SITE OF ACTION

Isoflurane and sevoflurane affected the ventilatory response to carbon dioxide through an exclusive action on parts of the peripheral chemoreflex loop (these are: peripheral chemoreceptors, sinus nerve and sites in the CNS related to the processing of peripheral input). In a previous study we performed the "wash-in" of isoflurane during steady-state isocapnic–hypoxia-driven ventilation.[4] Eighty per cent of the reduction in ventilation occurred within

Table 3 Hypoxic studies derived from the literature. n = Number of subjects, UCLA = University of California at Los Angeles. Isocapnia = ability to maintain isocapnia during hypoxic study; $\Delta P\text{E}'_{CO_2}$ is the difference of $P\text{E}'_{CO_2}$ between control and anaesthetic studies; anaesthetic response = (response during anaesthetic inhalation)/(control response). ns = drug response non-significantly different from control

Anaesthetic and institution	Anaesthetic concentration	*n*	Anaesthetic response	Isocapnia	$\Delta P\text{E}'_{CO_2}$ (kPa)	Ref.
Halothane						
Oxford University	0.05 MAC	12	0.65	Yes	0	15
	0.1 MAC	12	0.50	Yes	0	15
	0.2 MAC	12	0.25	Yes	0	15
University of Edinburgh	0.1% inspired	9	0.70	No	0.1	16
Leiden University	0.08% inspired	9	0.73	Yes	0	3
	0.15% inspired	9	0.72	Yes	0	3
	0.22% inspired	10	0.56	Yes	0.1	17
Enflurane						
Oxford University	0.04 MAC	12	0.73	Yes	0	18
	0.07 MAC	12	0.70	Yes	0	18
	0.13 MAC	12	0.45	Yes	0	18
	0.2 MAC	10	0.25	Yes	0	19
Isoflurane						
UCLA	0.1 MAC	8	0.94 (ns)	Yes	0	26
	0.1 MAC	8	0.85 (ns)	Yes	0	13
Karolinska Institute	0.85 MAC	8	1.50 (ns)	No	0.7	22
	0.6 MAC	7	0.49	Yes	0.5	23
	0.2% end-tidal	18	1.0 (ns)	Yes	0	24
University of Edinburgh	0.1 MAC	20	0.67	Yes	0	20
	0.1 MAC	9	1.15 (ns)	No	0.4	25
Leiden University	0.1 MAC	10	0.50	Yes	0	21
	0.1 MAC	8	0.53	Yes	0	4
	0.2 MAC	8	0.36	Yes	0	4
Desflurane						
Leiden University	0.1 MAC	14	0.94 (ns)	Yes	0	1
Sevoflurane						
Leiden University	0.1 MAC	11	0.70	Yes	0	2

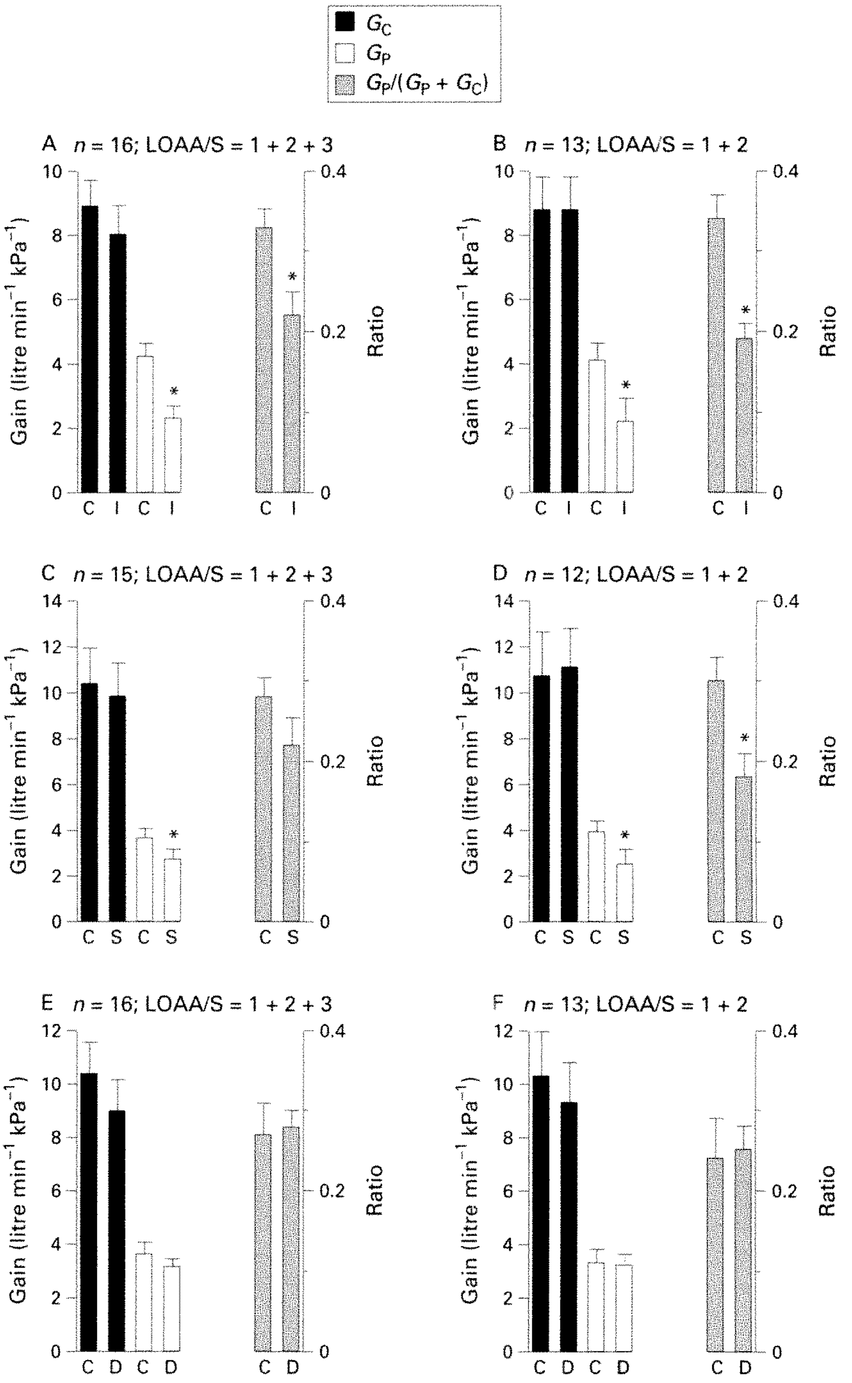

Figure 4 Mean (SEM) values of central carbon dioxide sensitivity (G_C), peripheral carbon dioxide sensitivity (G_P) and ratio ($G_P/(G_C + G_P)$) of isoflurane (I) (A and B), sevoflurane (S) (C and D) and desflurane (D) (E and F) studies (C = control). A, C and E = all subjects included; B, D and F = subjects included with Leiden observer's assessment of alertness/sedation (LOAA/S) scores 1 and 2. *$P < 0.05$ *vs* control.

the first 30 s of isoflurane wash-in. This suggests a selective depressant effect at the site of the peripheral chemoreceptors. However, at 30 s of wash-in some isoflurane may have reached the central nervous system. An additional effect on parts of the peripheral chemoreflex loop such as the sinus nerve or sites within the CNS may therefore not be excluded. Our study indicates that an effect at sites common to the peripheral and central chemoreflex loops is unlikely (i.e. integrating centres, motoneurones, intercostal nerves, phrenic nerves, diaphragm and intercostal muscles, lung, airways) as G_C remained unaffected (at least at LOAA/S levels 1 and 2, see below). When considering a possible action of low-dose isoflurane and sevoflurane at sites *within* the CNS, we speculate that different receptors or neurotransmitters, or both, may be involved in the central processing of afferent input from the peripheral and central chemoreceptors, resulting in marked differences in their resistance to low-dose anaesthetic agents.

INFLUENCE OF LEVEL OF SEDATION

We used a subjective sedation score to assess the level of central nervous system arousal (table 1). Comparison of this score with more objective measures of sedation (for example, the bispectral index of the EEG) indicated the usefulness of our scoring method.[2 30 31] However, we are aware that discrimination between scores is sometimes difficult (especially between scores 1 and 2), and therefore conclusions drawn from these data should be made with caution. We observed a significant relation between LOAA/S score and ΔG_C in the isoflurane and desflurane studies and Δratio in the sevoflurane studies. Further analysis revealed that ΔG_C and Δratio were significantly different in subjects with LOAA/S score 3 compared with those with scores 1 and 2 in the isoflurane and desflurane studies and sevoflurane studies, respectively (fig. 3). In other words, the three subjects with LOAA/S score 3 showed greater depression of G_C compared with G_P. Although we used equipotent concentrations in terms of MAC, these three subjects, all female, had a deeper level of sedation. Inter-individual differences in pharmacodynamics and possibly also differences between the sexes are the most likely explanation for the deeper level of sedation. Our small sample *suggests* that sedation by anaesthetics to levels sufficient to block the perception of or reaction to a light auditory stimulus (that is LOAA/S score > 2, an arousal state comparable with light sleep[2]) results in depression of the hypercapnic ventilatory response at sites within the central chemoreflex loop additional to sites within the peripheral chemoreflex loop. We stress the importance of stating the level of sedation of individual subjects when reporting data on ventilatory control and agents that affect the arousal state, because conclusions drawn from data at equi-MAC-fractions may differ significantly from those drawn at equi-sedative levels.

In summary, 0.1 MAC of isoflurane and sevoflurane, causing a CNS arousal state such that our subjects remained able to respond to a light auditory stimuli, affected the ventilatory control system via an exclusive effect on the peripheral chemoreflex loop. These observations are an extension of earlier findings of Knill and colleagues on isoflurane and halothane. At these concentrations and sedation levels, desflurane seemed exempt from an effect on ventilatory control. Our study suggests that at deeper levels of sedation, all three anaesthetics affected ventilatory control at sites within the central chemoreflex loop. Further studies are needed to investigate the influence of sedation of volatile anaesthetics, as opposed to the MAC of anaesthetics, on ventilatory control.

Acknowledgements

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Urinary excretion as an input variable in volume kinetic analysis of Ringer's solution

R. G. HAHN AND D. DROBIN

Summary

The disposition of fluid given by i.v. infusion can be studied by fitting one-volume and two-volume kinetic models to the fractioned dilution of blood haemoglobin and serum albumin concentrations over time. However, the two-volume model is sometimes associated with a high standard error in estimating the size of the secondary (peripheral) body fluid space, V_2. To examine if a fixed elimination rate constant (k_r) determined by urinary excretion can be used to make the model more stable, we infused Ringer's acetate 25 ml kg^{-1} over 30 min in 15 male volunteers (mean age 35 yr). A fixed k_r increased the total residual error when curve-fitting was applied according to the one-volume model. The two-volume model was improved when there was a strong within-patient covariance between k_r and V_2 ($r^2 \leq -0.98$). The size of V_2 was 10 litre when the fixed and model-generated values of k_r agreed fully. (*Br. J. Anaesth.* 1998; **80**: 183–188)

Keywords: model, pharmacokinetic; model, mathematical; fluid therapy; fluids, i.v.

Volume kinetics is a model for studying how the body handles fluid given by i.v. infusion.[1 2] Dilution of the plasma volume after i.v. infusion can be analysed and simulated over time in a manner similar to drug concentrations in pharmacokinetics.[3 4] The results are sensitive to analytical errors, however, and the choice of mathematical approach is relevant to the stability of the variable estimates.

The key problem is to estimate the size of the secondary (peripheral) fluid space, V_2, which can be overestimated owing to analytical errors in the assay used to quantify dilution of the primary (central) fluid space, V_1.[1] The precision of the estimate is also relatively poor.[3] Occasionally, it is difficult for the model to distinguish between elimination of fluid and distribution of fluid to V_2, which results in a low elimination rate constant (k_r) and an unrealistically large V_2. When this occurs, strong within-patient parameter covariances ($r^2 \leq -0.98$) indicate that k_r and V_2 behave as a single parameter. In these situations, the two-volume fluid space model has been considered invalid,[3] although it might be apparent from the dilution–time curve that the disposition of fluid occurs according to the two-volume model.

The purpose of this study was to evaluate if measured urinary excretion could be used as an input variable to make the volume kinetic model more stable, particularly with respect to V_2. The rationale for our attempt is that nearly all fluid indicated by k_r to be eliminated from the expanded fluid space can be collected as urine.[2] This allows the model to operate with k_r being set to a fixed value which is determined by urinary excretion. The result might be of practical value when using volume kinetic models. The models are also of theoretical interest for our understanding of body fluid volumes and kinetic constants involved in the disposition of crystalloid fluid.

Subjects and methods

After obtaining approved from the local Ethics Committee and informed consent, we studied 15 healthy men, aged 24–42 (mean 35) yr with a body weight of 65–100 (mean 77) kg.

After an overnight fast, volunteers rested comfortably on a bed, and at least 20 min of equilibration were allowed before the experiments were started between 08:00 and 09:00. A cannula was placed in the cubital vein of each arm for blood sampling and infusing fluid, respectively. Volunteers were given an i.v. fluid load consisting of Ringer's acetate solution 25 ml kg^{-1} (Pharmacia, Uppsala, Sweden) over 30 min via an infusion pump (Flo-Gard 6201, Baxter Healthcare, Deerfield, IL, USA). The ionic content of Ringer's solution was (mmol litre^{-1}): Na^+ 130, K^+ 4, Ca^{2+} 2, Mg^{2+} 1, Cl^- 110 and acetate 30. Monitoring of patients included arterial pressure measurements, pulse oximetry and electrocardiography (HP 56S, Hewlett Packard Co., MA, USA). Volunteers were allowed to void in the recumbent position during the study and in the standing position when the experiment had just been completed. Excreted volume of urine was recorded.

Venous blood (10 ml) was collected over 3 h. Samples were obtained every 5 min during the first 60 min and every 10 min thereafter. A tourniquet was not used. The first sample was obtained in duplicate and the mean value was used in calculations. Blood haemoglobin concentration (B-Hb) was measured on a Technicon H2 (Bayer, Tarrytown, NY, USA) using colorimetry at 546 nm. Serum albumin concentration was measured by dry chemistry based on the bromcresol green method followed by reflection spectrophotometry (Ektachem 250/950 IRC, Johnson and Johnson, Rochester, MI, USA). The duplicate samples

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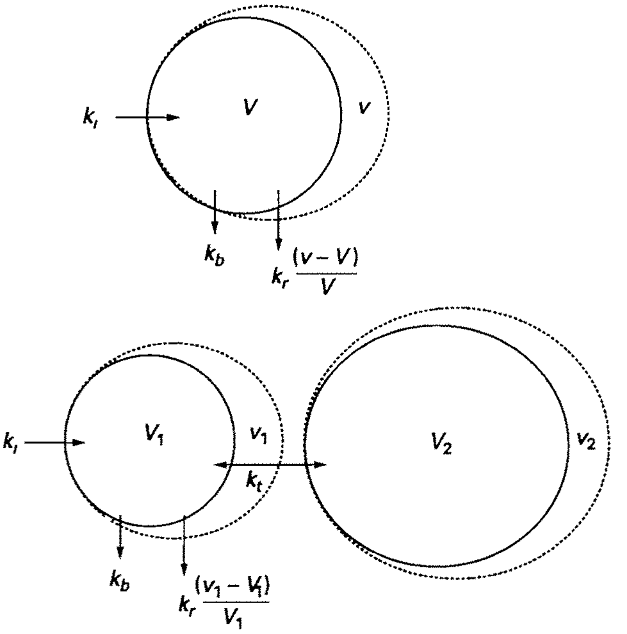

Figure 1 In the one-volume model (top), a fluid infused at a rate k_i is distributed in an expandable space with a volume (v), which the fluid space strives to maintain at an ideal (target) volume (V). Fluid leaves the space at a basal rate (k_b) and at a controlled rate proportional by a constant (k_r) to the deviation from the target volume. In the two-volume model (bottom), the primary fluid space communicates with a secondary fluid space. The rate of volume equilibration between the expandable fluid spaces (with volumes v_1 and v_2) is proportional to the relative difference in deviation from the target values (V_1 and V_2) by a constant (k_t).

obtained ensured a coefficient of variation of 1.0% for B-Hb and 2.7% for serum albumin.

The distribution of fluid given by i.v. infusion was analysed using volume-of-fluid-spaces kinetic models, which are summarized in figure 1. The infused fluid is assumed to occupy one or two expandable body fluid spaces and elimination occurs at a basal rate (perspiration and basal diuresis) and at a rate proportional to dilution of the central fluid space, V_1. The differential equations describing the volume changes in the expanded body fluid spaces and their matrix solutions are shown in the appendix.

Dilution of plasma volume (i.e. $(v_1—V_1)/V_1$), was used to quantitate fluid load. Plasma volume was chosen because extracellular fluid, but not erythrocytes, are expanded by the infused fluid. For this purpose, data on serum albumin were used directly. However, when the data on B-Hb were analysed, dilution of plasma volume was taken as the product of dilution of blood volume and (1–packed cell volume), where packed cell volume was assumed to decrease in proportion to the reduction in B-Hb. A correction for the loss of erythrocytes with blood sampling was always made.[1-3] The rate of spontaneous fluid loss from the expandable fluid space(s) (k_b) was set at 0.8 ml min^{-1}, which includes compensation for fluid loss associated with blood sampling. We have used previously a k_b value of 1.0 ml min^{-1}, but those volunteers ate a light meal before the experiments.[2]

The model parameters were calculated on a computer using Matlab version 4.2 (Math Works Inc., Notich, MA, USA) in which a non-linear least squares regression routine based on a modified Gauss–Newton method was repeated until no parameter changed by more than 0.001 (0.1%) in each iteration. Curve-fitting was performed on the one-volume fluid space model (VOFS1) where the output consists of the best estimates and standard errors for V and k_r. Calculations were then performed according to the two-volume fluid space model (VOFS2) where the output consists of the best estimates and standard errors for V_1, V_2, k_r and k_t. However, the results of VOFS2 were reported only if the F test indicated that it was statistically justified to fit a biexponential curve instead of a monoexponential one to the data.[5] An F value is obtained using the following equation:

$$F = [(MSQ_{VOFS1} — MSQ_{VOFS2})/MSQ_{VOFS2}] \times [df_{VOFS2} /(df_{VOFS1} — df_{VOFS2})]$$

where MSQ = mean square error for the difference between measured dilution of plasma volume and optimal curve fit according to VOFS1 and VOFS2, respectively; df = degrees of freedom, that is the number of data points used in fitting the function, minus the number of parameters fitted. The calculated value for F is compared with the critical value for significance in a standard statistical table.

All calculations were performed both when k_r was estimated together with the other parameters and also when k_r was set to a fixed value determined by

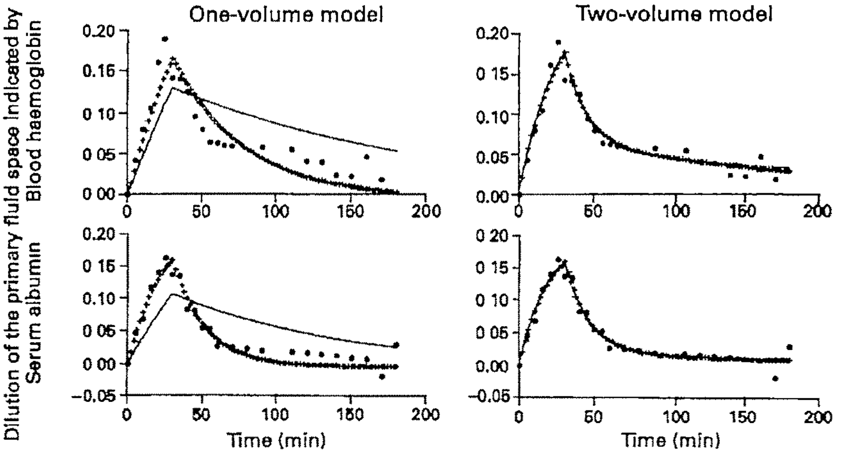

Figure 2 Volume kinetic curves from one experiment. When plasma dilution is indicated by both blood haemoglobin (top row) and serum albumin (bottom row) concentrations, the one-volume model (left) and the two-volume model (right) can generate a dilution–time curve using an elimination rate constant determined by the urinary excretion value (solid line) or by a value generated by the model (irregular line with crosses). In the latter case, the curves overlap although the model might give a lower k_r and a larger V_1.

Table 1 Kinetic analysis according to the one-volume fluid space model based on dilution–time data obtained during and after i.v. infusion of Ringer's solution 25 ml kg^{-1} over 30 min in 15 male volunteers. The first line for each variable gives the estimate and the second line its standard error. Data are median (25th and 75th percentiles). *Calculated from urine excretion. MSQ = Mean square error

	Urine excretion as input variable		
	With	Without	Wilcoxon test
Blood haemoglobin			
n	15	15	
V (litre)	8.69 (6.78, 10.48)	4.35 (4.01, 7.08)	$P<0.001$
	1.03 (0.71, 1.60)	0.47 (0.32, 0.61)	$P<0.002$
k_r (ml min^{-1})	77 (56, 112)*	176 (112, 208)	$P<0.001$
	None	11 (8, 19)	
MSQ (10^{-3})	89.3 (41.2, 100.3)	15.0 (11.6, 22.0)	$P<0.001$
Serum albumin			
n	15	15	
V (litre)	11.36 (9.12, 12.60)	7.84 (6.74, 9.47)	$P<0.01$
	0.91 (0.77, 1.24)	0.69 (0.52, 0.83)	$P<0.01$
k_r (ml min^{-1})	59 (44, 67)*	98 (91, 121)	$P<0.001$
	None	10 (9, 13)	
MSQ (10^{-3})	41.0 (33.6, 52.4)	21.3 (18.1, 28.2)	$P<0.001$

total urinary excretion during the experiment. To calculate k_r, the excreted volume of urine was divided by the integral of the dilution–time curve after assuming that half of the spontaneous elimination of fluid (k_b) also appeared as urine.

Data are presented as median (25th and 75th percentiles). Differences between methods of analysis were studied by the Wilcoxon matched pair test and the Mann–Whitney *U* test, as appropriate. Correlations between parameters were evaluated by linear regression, where r = correlation coefficient. $P < 0.05$ was considered statistically significant. Five of the 15 experiments have been used in another report.[5]

Results

Dilution of B-Hb and serum albumin concentrations increased during the infusions and decreased promptly during the first 30 min after the infusion was completed. Thereafter, dilution was usually restored more slowly (fig. 2). Total urinary excretion was 950 ml (25th and 75th percentiles 718, 1067 ml, respectively).

Use of the urinary excretion value to calculate k_r markedly increased the mean square error (MSQ) obtained when the one-volume model was fitted to the data, when both B-Hb and serum albumin were used to indicate dilution of plasma volume (table 1, fig. 2). The target volume, V, and the standard error associated with this estimate, became larger. The model-predicted k_r was markedly higher than the k_r obtained from the urine data.

The two-volume model was also applied, and we report the experiments in which this model was statistically justified. Here, application of the urine excretion-generated k_r also increased MSQ, but the difference was not great (table 2). Little difference was seen when the two curve fits were compared graphically (fig. 2, right). The parameter standard errors were significantly reduced by applying a fixed k_r

Table 2 Analysis of the same data as in table 1 using the two-volume fluid space model. The experiments are reported in which the application of a biexponential curve instead of a monoexponential curve was statistically justified (partial *F* test). *Calculated from the urine excretion. MSQ = Mean square error

	Urine excretion as input variable		
	With	Without	Wilcoxon test
Blood haemoglobin			
n	8	9	
V_1 (litre)	3.43 (2.89, 4.23)	3.37 (2.79, 4.10)	
	0.41 (0.25, 1.04)	0.56 (0.37, 1.14)	$P<0.02$
V_2 (litre)	16.3 (10.1, 20.0)	4.49 (4.22, 12.38)	$P<0.05$
	2.60 (0.99, 4.54)	2.46 (1.87, 3.22)	
k_t (ml min^{-1})	231 (125, 298)	206 (111, 315)	
	26 (14, 61)	44 (26, 130)	$P<0.03$
k_r (ml min^{-1})	77 (56, 112)*	104 (70, 144)	$P<0.03$
	None	15 (11, 22)	
MSQ (10^{-3})	6.9 (5.5, 10.0)	6.3 (5.1, 8.9)	$P<0.03$
Serum albumin			
n	15	13	
V_1 (litre)	4.28 (3.45, 4.65)	4.31 (3.21, 4.57)	
	0.49 (0.34, 0.75)	0.61 (0.37, 0.86)	$P<0.01$
V_2 (litre)	11.20 (8.27, 12.25)	10.72 (7.92, 14.20)	
	0.89 (0.73, 1.33)	2.54 (1.26, 9.91)	$P<0.03$
k_t (ml min^{-1})	209 (178, 336)	274 (173, 367)	
	30 (19, 67)	48 (27, 114)	$P<0.02$
k_r (ml min^{-1})	59 (44, 67)*	53 (36, 69)	
	None	15 (10, 45)	
MSQ (10^{-3})	6.8 (3.1, 11.7)	6.5 (2.7, 11.3)	$P<0.02$

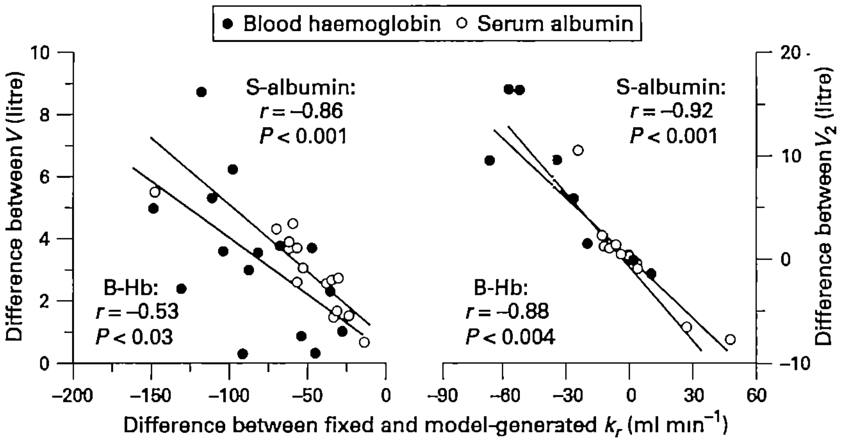

Figure 3 Difference between the elimination rate constant k_r, as determined by urinary excretion and generated by the kinetic model, *vs* the difference in target volume V in the one-volume model (left) and the secondary fluid space V_2 in the two-volume model (right).

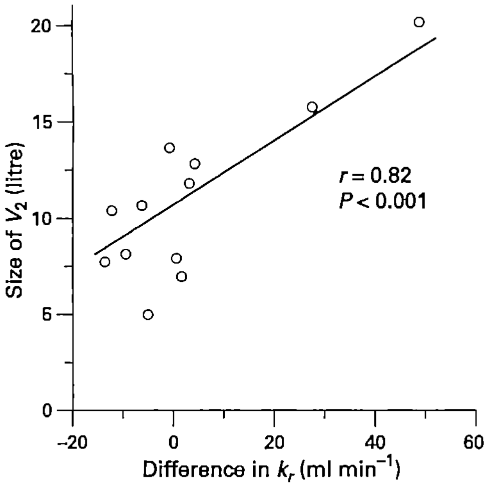

Figure 4 Difference between elimination rate constant k_r, as determined by urinary excretion and generated by the kinetic model, *vs* the size of V_2 in the two-volume model. Each circle represents one experiment in which plasma dilution is indicated by the serum albumin concentration. One extreme outlier has been omitted. The plot indicates that V_2 is approximately 10 litre when both methods for determining k_r agree fully.

Table 3 Volume kinetic variables in the two-volume fluid space model based on analysis of serum albumin data, depending on whether there is a strong within-patient covariance between k_r and V_2. The data shown are the size of V_2 and the standard error associated with this estimate, and Δk_r which is the difference between the k_r from the urinary excretion and that obtained from the model

	Covariance between k_r and V_2		Mann–Whitney test
	$r > -0.98$	$r \leqslant -0.98$	
n	9	4	
V_2 (litre)	8.16 (7.52, 11.26)	17.99 (14.34, 20.86)	P<0.02
Error	1.41 (1.16, 2.58)	16.04 (11.00, 37.21)	P<0.01
Δk_r (ml min^{-1})	5 (1, 10)	26 (15, 38)	P<0.05

instead of allowing k_r to be estimated by the model, the only exception being the error associated with estimate of V_2. However, the error of V_2 became significantly reduced when the standard error *relative* to the size of V_2 (i.e. the standard error divided by V_2) was studied.

The difference between the fixed and model-generated values of k_r correlated inversely with the differences in target volumes (V or V_2) obtained in the same analyses; the regression line runs through zero in the plots for both the one-volume (fig. 3, left) and two-volume (fig. 3, right) models. The size of the model-generated V_2 is expected to be approximately 10 litre (130 ml kg^{-1}) when there is full agreement between the model-generated k_r and the value calculated from urinary excretion (fig. 4).

The experiments which generated data deviating markedly from the zero intercept in figure 3 were characterized by strong within-patient covariances between k_r and V_2 ($r^2 \leqslant -0.98$). When a solution to the two-volume model was obtained and the curve fit appeared to be statistically justified, such a high covariance between k_r and V_2 was found in four of the experiments based on dilution of serum albumin (table 3). In these cases, the absolute size of V_2 and the standard error associated with this estimate were much larger than in the other experiments.

Discussion

Volume kinetics may become an important tool to optimize fluid therapy in surgery and trauma care in the future.[1-4] This approach provides knowledge on how plasma volume expansion during and after i.v. infusion of fluid changes over time. For example, the values obtained for the model parameters in tables 1 and 2 can be entered into a computer and, using the mathematical solutions presented in the appendix, simulate the dilution–time profile after any infusion rate or combinations of infusion rates of Ringer's solution. Furthermore, as dilution stems only from the infused fluid, the size of the body fluid spaces expanded by crystalloid fluid and the rates of exchange of fluid between these spaces, under optimal conditions, may be close to the real volumes and rates.

This study was designed to evaluate if volume kinetic models can be made more stable by using the urinary excretion value as an input variable in the calculations. This might be achieved by calculating the elimination rate constant (k_r) from the excreted volume of urine and the area under the curve of the dilution of B-Hb or serum albumin concentrations during and after i.v. infusion of Ringer's solution.

However, the results showed that the models usually did not become more stable when this was done. In the one-volume model, the use of a fixed k_r increased the mean square error associated with the curve-fitting and the standard error involved in estimating the size of the single expanded body fluid space. This implies no benefit. The curve fit shown in figure 2 also illustrates clearly that the k_r fixed by urinary excretion was a poor estimator of the shape properties of the dilution curve. When the two-volume model was applied to the data, however, the shape of the dilution curve appeared very similar when the fixed and model-predicted values of k_r were used. The parameter standard errors became reduced when using a fixed k_r, but the improvements were approximately those expected when determining three parameters instead of four. Although significant, the improved precision was not large enough to warrant a new practice for performing these calculations.

There is one special situation, however, when the use of a fixed k_r seems to be warranted. When the *F* test indicates that the two-volume model is statistically justified but the conventional method of obtaining model-generated estimates of all four parameters shows a strong within-patient covariance between V_2 and k_r (r between −0.98 and −1.00), the size of V_2 is given with so poor a precision that the estimate does not contain any real information. In these cases, the model-generated value of k_r differs considerably from that indicated by urinary excretion. When this situation occurs, it would be justified to use urinary excretion to calculate k_r, because this is a better choice than to accept the optimal curve fit generated by the one-volume model. In our study, we found such strong covariances only when dilution of V_1 was indicated by serum albumin concentration, but in subsequent experiments we have confirmed that the "galloping" V_2 can be found also when B-Hb concentration is used.

Comparison between the values of V_2 and k_r obtained when using a fixed k_r offered some further theoretical basis for the "true" size of V_2. When the model-generated k_r differs from the fixed value, the size of V_2 is also likely to differ by a magnitude that is predictable. A plot of these differences indicates that the zero difference between the two analytical approaches corresponds to a size of V_2 of approximately 10 litre. This size should represent the most accurate estimate of the volume of the peripheral fluid space that is expanded by the infused fluid. However, our view is valid only if k_r represents urinary excretion and that the difference between the two values of k_r is correct.

The volume of 10 litre for V_2 was a few litres less than the expected size of the interstitial fluid volume, but is not unreasonable as the interstitial fluid space of the central nervous system and bone tissue can hardly be expanded by Ringer's solution. It should be emphasized that the size of an expandable fluid space can only be determined by expanding it. This volume is not available for measurement by tracer techniques. Although not elaborated upon in this study, the reader should observe that some experiments are better explained by a one-volume kinetic model than by a two-volume one, and that the total size of the expandable body fluid space in those cases is usually smaller compared with when the two-volume model is justified.[2 3]

The other parameters in the two-volume model were less affected than V_2 and k_r when the urinary excretion value was used as an input variable. The size of the primary (central) fluid space, V_1, was 3.4–4.3 litre, which suggests that it corresponds to plasma volume. These parameters were estimated with a standard error of approximately 10%, although the error was somewhat larger when k_r was generated by the model. The constant k_t, which governs diffusion of fluid between the primary and secondary fluid spaces, did not differ significantly depending on whether or not a fixed k_r was applied.

The problem with a strong covariance between V_2 and k_r stems in part from the choice of method used to perform the volume kinetic analysis. The first approach used was the random search method which tests different parameter values to minimize the squared difference (MSQ) between a model-generated curve and the experimental data.[1 2] The iterations continue until no further improvement of the fit is obtained in 15 trials. The second approach, which is based on matrix algebra to facilitate future modifications of the model, also repeats an algorithm until the MSQ is minimized. However, the model works by adding corrections to the previous parameter values, and the corrections are based on the derivative of a gradient function. No testing of random values is involved. The model continues to search for the optimal parameter values until none is changed by more than 0.1% in each iteration. The confidence interval for the minimum represents an ellipsoid area in the parameter space, and the precision of the parameter value can be poor if this area is very long and narrow.[3 4]

The "galloping" V_2 implies that the iterations continue with a progressive increase in V_2 and a decrease in k_r when MSQ is already very low. This problem did not occur with the random search method, but we have realized that the precision of V_2 given by this algorithm is always poor in the experiments where the Gauss–Newton method results in a "galloping" V_2. Thus there is a need for making the two-volume model more stable in certain experiments when the random search method is also used. Good precision of the parameter estimates is essential if we wish to improve our understanding of the real body fluid volumes and kinetic constants involved in the disposition of crystalloid fluid.

In summary, the urinary excretion value can be used to make the two-volume kinetic model more stable in cases where the correlation matrix indicates strong within-patient covariance between V_2 and k_r. This approach is not clearly justified in other situations.

Appendix

A fluid given by i v. infusion at a rate k_i is distributed in an expandable space with a volume (v), which the fluid space strives to maintain at an ideal (target) volume (V). Fluid leaves the space at a basal rate, representing perspiration and baseline diuresis (k_b, fixed at 0.8 ml min^{-1}), and at a controlled rate proportional by a constant (k_r) to the deviation from the target volume. The following differential equation describes the situation for the single-volume fluid space model (fig. 1, top):

$$dv/dt = k_i - k_b - k_r\,(v-V)/V$$

A two-volume space model was also developed in which the primary fluid space communicates with a secondary fluid space. The net rate of fluid exchange between the expandable fluid spaces (with volumes v_1 and v_2) is proportional to the relative difference in deviation from the target values (V_1 and V_2) by a constant (k_t) (fig. 1, bottom). Also, in the two-volume model, the system strives to maintain the target volumes by acting on the controlled elimination mechanism in proportion, k_r, to the relative deviation from the target volume of the primary fluid space. The following system of differential equations describes the situation:

$$\frac{dv_1}{dt} = k_i - k_b - \frac{k_r(v_1 - V_1)}{V_1} - k_t\left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2}\right]$$

$$\frac{dv_2}{dt} = k_t\left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2}\right]$$

The mathematical models describing the one-volume and two-volume models are linear differential equations with constant coefficients and their solutions can be given analytically in different forms. The single fluid space model is easily solved as a monoexponential solution.[1 4] The solution of the two-volume fluid space model used in this study is based on the matrix exponential e^{At}. During infusion (d) we have

$$\begin{pmatrix} w_{1d}(t) \\ w_{2d}(t) \end{pmatrix} = [(k_i - k_b)/k_r](I - e^{At}) \begin{pmatrix} 1 \\ 1 \end{pmatrix} \qquad 0 \leq t \leq t_1$$

and after infusion

$$\begin{pmatrix} w_{1a}(t) \\ w_{2a}(t) \end{pmatrix} = (-k_b/k_r)(I - e^{A(t-t_1)}) \begin{pmatrix} 1 \\ 1 \end{pmatrix} + e^{A(t-t_1)} \begin{pmatrix} w_{1d}(t_1) \\ w_{2d}(t_1) \end{pmatrix}$$

$$t_1 \leq t \leq \infty$$

where the matrix A is

$$A = \begin{pmatrix} -(k_r + k_t)/V_1 & k_t/V_1 \\ k_t/V_2 & -k_t/V_2 \end{pmatrix}$$

This form is well suited for numerical computation using, for example, the mathematical program Matlab, which has the matrix exponential e^{At} implemented as a standard function.

Acknowledgements

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Bovine haemoglobin-based oxygen carrier for patients undergoing haemodilution before liver resection

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Summary

We have studied the use of ultrapurified polymerized bovine haemoglobin (HBOC-201) in patients undergoing preoperative haemodilution before liver resection. After autologous blood donation of 1 litre, 12 patients (six males, six females, mean age 59 (35–69) yr) received Ringer's lactate solution 2 litre and, in a random design, 6% hydroxyethyl starch 70 000/0.5 (HES) 3 ml kg^{-1} or HBOC-201 0.4 g kg^{-1} within 30 min. Blood samples were obtained for blood chemistry, co-oximetry, haematology, coagulation profiles and immunology examinations before operation, on the day of surgery, on days 2–4 and 7 after operation, on the discharge day and 3 months after operation. There were no differences in patient characteristics, blood loss, amount of solutions infused, transfused allogeneic blood or duration of hospital stay. There were no local or systemic allergic reactions with infusion of HES or HBOC-201. Patients receiving HBOC-201 developed more pronounced leucocytosis and reticulocytosis during the early postoperative days compared with HES-treated patients. The mean maximum plasma haemoglobin concentration was 1.0 (SD 0.2) g dl^{-1} at the end of infusion of HBOC-201. The mean intravascular half-life of HBOC-201 was 8.5 h. Patients in both groups experienced temporary changes in liver enzymes and coagulation variables which returned to normal before discharge. Urinalysis revealed no difference between groups and no free haemoglobin was detected in urine. Patients receiving HBOC-201 showed no IgE and only a slight increase in IgG titres to HBOC-201 on the day of discharge; these were not detectable at 3 months. Single-dose administration of HBOC-201 was well tolerated by patients undergoing elective liver resection surgery and appears to be safe as a substitute during preoperative haemodilution. (*Br. J. Anaesth.* 1998; **80**: 189–194)

Keywords: blood, substitutes; blood, replacement; blood, haemoglobin; fluids, i.v.; fluid therapy; blood, haemodilution; surgery, hepatic

Technical progress in the purification and formulation of haemoglobin solutions has resulted in the production of oxygen carriers which are free of toxic side effects on the liver and kidneys. Animal studies in different species have shown that a novel ultrapurified polymerized bovine-derived haemoglobin does not cause severe side effects on the liver, kidney or coagulation,[1 2] even in doses higher than those used clinically.[3] In addition, this bovine haemoglobin solution has a calculated relative potency of three times that of red blood cells (RBC) in restoring tissue oxygenation.[4] A phase I study in normal volunteers showed that polymerized bovine haemoglobin had a dose-dependent intravascular half-life of 16 h.[5]

Several studies have shown that patients with different tumours had a shorter disease-free survival and higher incidence of recurrent or metastatic cancer if they received perioperative allogeneic blood transfusions.[6 7] There is also evidence that the rate of postoperative infection is higher in patients after homologous red cell transfusion than in patients who were not transfused.[8] As a consequence, perioperative blood substitution with haemoglobin solutions may be advantageous in cancer patients by reducing the amount of allogeneic blood transfusions. As animal data indicate that bovine haemoglobin could enhance the amount of preoperatively donated blood[9] this material may have an indication in cancer patients who are normally excluded from predonation of autologous banked red cells.

This prospective, randomized study was designed to examine the safety and tolerance of a moderate dose of bovine haemoglobin compared with hydroxyethyl starch when used during acute preoperative blood donation in patients undergoing liver resection.

Patients and methods

After obtaining Ethics Committee approval and informed consent, we studied 12 patients (six males, six females, mean age 59 (range 35–69) yr, ASA I–II) undergoing elective liver resection surgery. Exclusion criteria were severe cardiovascular disease (e.g. uncontrolled hypertension >180/100 mm Hg, recent myocardial infarction <6 months, unstable angina, congestive heart failure), decompensated pulmonary disease or porphyria. Patients suffering from acute or chronical hepatic infections (e.g. hepatitis B and C), liver cirrhosis, anaemia (preoperative packed cell volume <30% or haemoglobin <10 g dl^{-1}) or allergic reactions to beef products were also excluded.

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Table 1 Specifications of HES and HBOC-201

	HES	HBOC-201
Molecular weight	70 000	32 000–500 000
Colloid osmotic pressure (mm Hg)	24	17
Osmolarity (mosmol kg^{-1})	320	290–310
Viscosity 37° (mPa s)	1.4–1.5	1.30
pH	5.0–7.0	7.6–7.9
P_{50} (kPa)		4.8–5.1
Hb (g dl^{-1})		13 (1)
Sodium (mmol litre^{-1})	154	145–160
Potassium (mmol litre^{-1})	0	3.5–5.5
Chloride (mmol litre^{-1})	154	105–120
Calcium (mmol litre^{-1})	0	0.5–1.5
Endotoxin (EU ml^{-1})		<0.5
Phospholipid (nmol ml^{-1})		<3

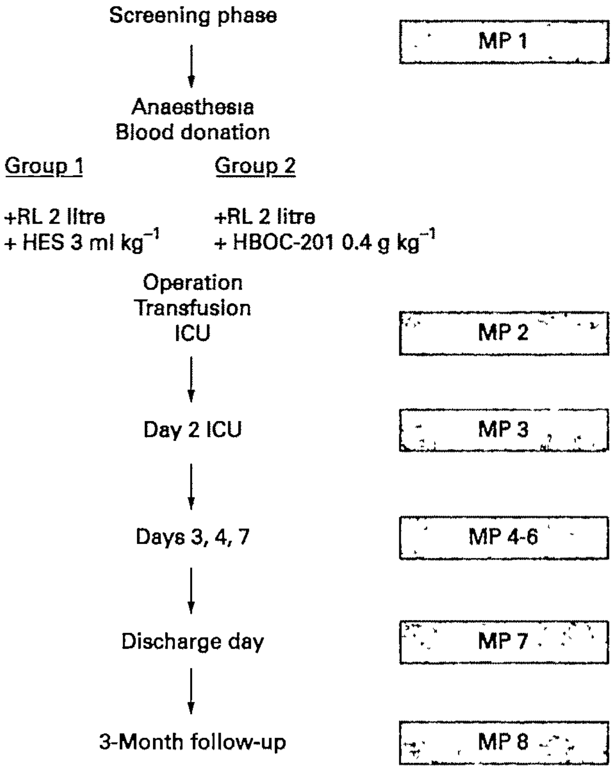

Figure 1 Study design. RL = Ringer's lactate solution; HBOC-201 = ultrapurified, glutaraldehyde polymerized bovine haemoglobin; HES = hydroxyethyl starch 70,000/0.5.

All patients underwent a screening examination 1–3 days before operation. On the day of surgery, patients were premedicated with midazolam 7.5 mg orally, 1 h before arriving in the anaesthesia room where they were monitored by ECG, non-invasive arterial pressure measurement and pulse oximetry. General anaesthesia was induced with fentanyl 3 µg kg^{-1}, etomidate 0.3 mg kg^{-1} and vecuronium 0.1 mg kg^{-1}. After tracheal intubation the lungs were ventilated mechanically with 70% nitrous oxide in oxygen. Anaesthesia was maintained with 0.6–0.8 vol% isoflurane and repeated i.v. injections of fentanyl 0.1 mg and vecuronium 2 mg.

Two large peripheral i.v. cannulae were inserted for autologous blood donation and infusion of the respective substitute. A radial cannula, central venous and urinary catheters were inserted. After autologous blood donation of 1 litre and infusion of lactated Ringer's solution 2 litre, patients received in a random manner within 30 min, hydroxyethyl starch (HES) 70,000/0.5 (Rheohes, B. Braun, Germany) 3 ml kg^{-1} (group 1) or ultrapurified, glutaraldehyde polymerized bovine haemoglobin (HBOC-201, Biopure, Cambridge, USA) 0.4 g kg^{-1} (group 2) (table 1).

Blood-gas tensions were measured with an ABL 505 (Radiometer, Denmark). Oximetry was performed using the OSM 3 (Radiometer, Denmark). Plasma haemoglobin concentrations were measured after 5 min of centrifugation (4000 rpm, Heraeus Sepatech) of arterial blood which was stabilized with ethylenediamine tetra-acetic acid (EDTA). Total haemoglobin concentration was also measured in EDTA-stabilized arterial blood by the haemoglobin cyanide method. Haematology, white blood cell differential and platelets were measured in a standardized blood smear of arterial EDTA-stabilized blood samples by microscopy. Coagulation variables (Quick's value, activated partial thromboplastin time (APTT) and fibrinogen) were measured by specific tests. A Hitachi 747 autoanalyser was used for measurement of blood chemistry. At every measurement time (MP 1–8), 10 ml of urine were aspirated from the urinary catheter and examined for free haemoglobin concentration, pH, glucose, protein, ketones, red and white cells, epithelial cells and casts. Immunological samples were obtained on the day before surgery, on postoperative day 7, on the day of discharge and 3 months after surgery.

Blood loss, and amount of crystalloids and colloids infused were monitored during operation and the amount of transfused allogeneic blood within postoperative days 1–7. All patients received their own donated blood when intraoperative haemoglobin concentrations were <7.5 g dl^{-1} or at the end of operation. Duration of postoperative artificial ventilation in the ICU and duration of hospital stay were recorded.

All measurements were performed before surgery (MP 1), 4 h after surgery in the ICU (MP 2), on the morning of postoperative days 2–4 and 7 (MP 3–6), and on the day of discharge (MP 7). A follow-up examination was performed 3 months after operation (MP 8) (fig.1).

Data are reported as mean (SD). Patient data in both groups were tested by the Mann–Whitney *U* test. Differences within groups were tested by ANOVA for repeated measurements and *post hoc* comparison by Student's *t* test. Differences between groups were tested by the Wilcoxon test or two-way ANOVA and *post hoc* Bonferroni's correction for alpha. All differences were considered significant at $P < 0.05$.

Results

Patient characteristics and data on perioperative fluid management are given in table 2. After autologous

Table 2 Patient characteristics and perioperative data (mean (SD) [range] or number)

	HES	HBOC-201
n	6	6
Age (yr)	60 [56–69]	53 [35–62]
Sex (M/F)	5/1	3/3
Height (cm)	172 (4) [169–178]	171 (10) [157–183]
Weight (kg)	78 (9) [70–95]	76 (14) [56–91]
ASA class I/II	0/6	3/3
Operation time (min)	213 (105)	236 (82)
Blood loss (litre)	1.1 (1.5)	1.5 (1.1)
Crystalloids (litre)	1.8 (1.3)	2.2 (1.6)
Colloids (ml)	817 (444)	1020 (593)
RBC (ml)	300 (735)	467 (628)

Table 3 Haematology and oximetry data (mean (SD)) after preoperative haemodilution with HES or HBOC-201 in liver resection patients. PCV=Packed cell volume; Hb=total arterial haemoglobin concentration; Hbf=plasma haemoglobin concentration; MetHb=arterial methaemoglobin concentration; WBC=white blood cell count; Reti.=reticulocyte count. MP 1=screening; MP 2=4 h after operation, day of surgery; MP 3=day 2; MP 4=day 3; MP 5=day 4; MP 6=day 7; MP 7=discharge day; MP 8=3-month follow-up. *P<0.05 *vs* MP 1 (screening); †P<0.05 *vs* group 1 (HES)

Normal range		PCV (vol %) M·38–52 F:37–46	Hb (g dl^{-1}) M:14–18 F:12–16	Hbf (g dl^{-1}) 0	MetHb (%) ≤1	WBC (×10^9 litre^{-1}) 4.3–10.0	Reti. (%) 0.7–1.5
MP 1	HES	39.2 (3.5)	13.2 (1.4)	0 (0)	0.4 (0.2)	6.1 (1.2)	1 1 (0 4)
	HBOC	34.5 (4.3)	11.7 (1.5)	0 (0)	0.5 (0 2)	5.8 (1.6)	1 6 (0.7)
MP 2	HES	36.0 (4.1)	11.9 (1.2)	0 (0)	0.5 (0.1)	9.9 (1.7)*	1 7 (0.5)*
	HBOC	32.7 (6.1)	11.0 (2.1)	0.4 (0.2)*†	1.1 (0.2)*†	10.9 (3 6)*	1.7 (0.5)
MP 3	HES	33.9 (3 6)*	11.3 (1.4)	0 (0)	0 6 (0.1)*	5.4 (0.9)	1.6 (0.8)
	HBOC	29.6 (5.0)	10.0 (1.7)	0 22 (0.1)*†	1.2 (0.3)*†	10.9 (3.5)*	1.2 (0.3)
MP 4	HES	31.3 (4.7)*	10.5 (1.8)*	0 (0)	0.5 (0.1)	9.7 (5.1)	1.6 (0.4)
	HBOC	30.8 (4 2)	10.3 (1.4)	0.1 (0.0)	1.0 (0.6)	13.6 (5 7)*	2.0 (0.6)*
MP 5	HES	30.4 (4.7)*	10.2 (1.6)*	0 (0)	0.4 (0.2)	8.1 (4.8)	1.4 (0.4)
	HBOC	29 1 (4.0)*	9.8 (1 3)*	0.02 (0.04)	0.6 (0.2)	11.0 (2.7)*	1.9 (0.4)†
MP 6	HES	33.2 (4.9)*	11.3 (1.0)*	0 (0)	0.5 (0.2)	15.2 (11 8)	3.4 (2.0)
	HBOC	32.2 (2.2)	10 4 (0.8)	0.02 (0.04)	0.4 (0.2)	10.5 (6.4)	2.9 (1.8)
MP 7	HES	30.1 (2.8)*	9.9 (1.2)*	0 (0)	0.6 (0.1)	10 5 (5.4)	3.9 (1 6)
	HBOC	31.9 (2.6)	10.5 (0.9)	0 (0)	0.6 (0.2)	10.1 (5.2)	3 9 (1 8)
MP 8	HES	43.2 (3.9)	14.2 (1.3)	0 (0)	0 4 (0.1)	6.2 (1.4)	1.6 (0.7)*
	HBOC	41.5 (4.3)	13.2 (1.1)	0 (0)	0 3 (0.0)	5.4 (1.6)	1.6 (0.5)

blood donation, patients in group 1 received HES 241 (29) ml and in group 2 HBOC-201 233 (44) ml. No local or systemic allergic reactions were detected during infusion of HES or HBOC-201. Two patients in each group underwent resection of one or two liver segments; two patients in group 1 and three patients in group 2 received a left or right hemi-hepatectomy. Because of unexpected tumour spread, resection was not possible in two patients in group 1 and in one patient in group 2.

There were no differences in heart rate, ventilatory frequency, temperature, pulse oximetry or blood-gas tensions between groups at any time. However, on admission to the ICU (MP 2), patients in group 2 had a higher mean arterial pressure than those in group 1 (95 (18) *vs* 83 (11) mm Hg; $P = 0.037$).

Plasma haemoglobin concentration peaked at 1.0 (0.2) g dl^{-1}, 30 min after the start of infusion of HBOC-201 and showed a decrease to 0.22 (0.1) g dl^{-1} on the morning of day 2 (table 3). The extrapolated intravascular half-life of HBOC-201 was 8.5 h.

In contrast with group 1, the concentrations of total arterial methaemoglobin increased after operation in group 2 with the maximum on day 2. The increase in leucocytes on postoperative days 2–4 and reticulocytosis on day 3 were more pronounced in the HBOC-201 group compared with baseline values than in the HES group (table 3).

Haemodilution and operation-dependent decreases in coagulation occurred; these returned to baseline values within 7 days after surgery (table 4). There were no differences between groups.

There were no differences in blood chemistry between groups (table 4, figs 2–4). All HES patients were negative for both IgG and IgE to HBOC-201. No IgE antibody responses to HBOC-201 were detected in group 2. Five of six patients in group 2 developed clinically insignificant titres to HBOC-201, and IgG was undetectable 3 months after infusion.

Urinary output did not differ between the two groups during the early postoperative period. Free

Table 4 Coagulation profiles and blood chemistry (mean (SD)) after preoperative haemodilution with HES or HBOC-201 in liver resection patients. Quick =Quick's value; APTT=activated partial thromboplastin time; Fibrinogen=fibrinogen concentration; Thrombo.=platelet count; Amylase=pancreatic amylase; LDH=lactate dehydrogenase, GGT=gamma-glutamyl transpeptidase. MP 1=screening; MP 2=4 h after operation, day of surgery, MP 3=day 2; MP 4=day 3, MP 5=day 4; MP 6=day 7; MP 7=discharge day; MP 8=3-month follow-up *P<0.05 *vs* MP 1 (screening)

Normal range		Quick (%) 70–130	APTT (s) 25–47	Fibrinogen (mg dl^{-1}) 150–450	Thrombo. (×10^9 litre^{-1}) 150–350	Amylase (iu litre^{-1}) 13–64	LDH (iu litre^{-1}) 120–240	GGT (iu litre^{-1}) 6–28
MP 1	HES	107 (15)	32.0 (4.3)	398 (73)	232 (68)	39 3 (20)	177.2 (40 7)	56.9 (61 2)
	HBOC	108 (20)	30.7 (2 3)	406 (120)	254 (60)	31.8 (3.6)	186.2 (51.7)	110.4 (112.3)
MP 2	HES	80 (15)*	38 0 (7.1)	264 (70)*	169 (56)	69.7 (28.6)	325.3 (88 4)*	31.2 (19.3)
	HBOC	73 (17)*	40.0 (6.2)*	245 (132)	200 (57)	126.7 (219.9)	331.4 (59.8)*	54 4 (53.7)
MP 3	HES	92 (13)*	38 0 (2.6)*	289 (56)	208 (62)	102.3 (40.0)	373.0 (150 5)*	31.5 (20 1)
	HBOC	86 (14)	37.8 (1.6)*	262 (86)	216 (49)	133.0 (132.9)	446.0 (234.4)*	45 0 (44 3)
MP 4	HES	68 (22)*	45.2 (8.6)*	485 (199)	149 (58)*	52.5 (19.3)	252.2 (65.2)*	30.7 (22.7)
	HBOC	52 (24)*	52.7 (13.7)	449 (267)	177 (37)*	84.5 (58.5)	289.5 (87.5)*	44.2 (40.2)
MP 5	HES	81 (20)*	43.2 (9.9)*	532 (175)	149 (53)*	41.3 (16.7)	222 7 (64.8)	35 2 (28.9)
	HBOC	73 (35)	45.0 (8.6)*	503 (339)	177 (46)*	58.0 (35.6)	260.7 (105.3)	41 8 (31.3)
MP 6	HES	94 (18)	34.6 (7.9)	534 (210)	284 (96)	140 7 (93.2)	290.3 (45.7)	91.0 (23.5)
	HBOC	70 (32)*	50.5 (29.4)	450 (244)	286 (98)	63.6 (46.3)	261.4 (82.4)	117.8 (23.6)
MP 7	HES	79 (26)	44.0 (6.6)*	508 (237)	329 (149)	92.0 (61.2)	220.0 (34.6)	57.3 (33 5)
	HBOC	85 (29)	39.4 (11.9)	456 (166)	275 (64)	98.7 (67.1)	239.5 (34.9)	151 5 (105)
MP 8	HES	111 (14)	34.2 (3.3)	476 (180)	250 (49)	46.8 (34.5)	195.2 (48.1)	60.8 (51.4)
	HBOC	112 (12)	32.6 (2.1)	360 (126)	237 (58)	32.0 (4.7)	152.2 (9.5)	152.2 (9.5)

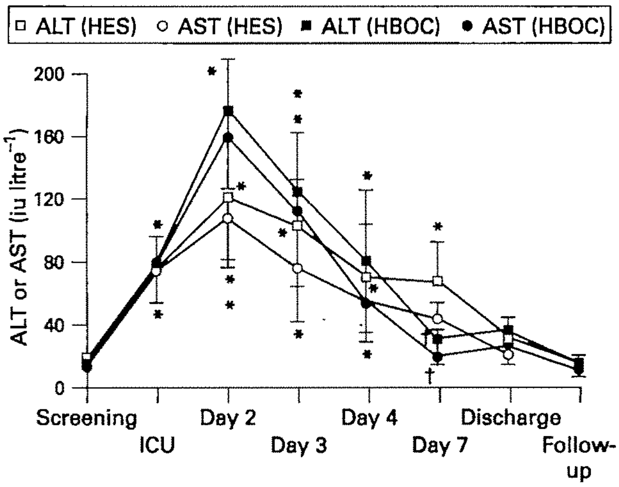

Figure 2 Changes in concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) after preoperative haemodilution with HES or HBOC-201 in liver resection patients. Values are mean (SEM). $*P < 0.05$ *vs* screening; $\dagger P < 0.05$ *vs* HES.

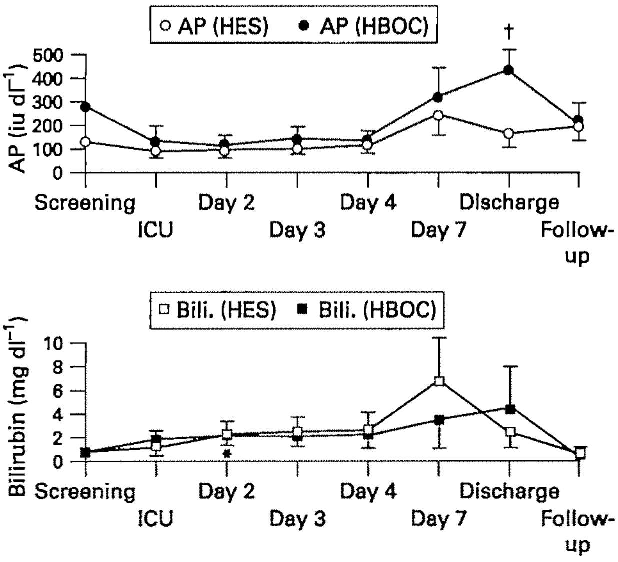

Figure 3 Changes in concentrations of alkaline phosphatase (AP) and bilirubin (Bili.) after preoperative haemodilution with HES or HBOC-201 in liver resection patients. Values are mean (SEM). $*P < 0.05$ *vs* screening; $\dagger P < 0.05$ *vs* HES.

haemoglobin was not detected in urine over time. Urinalysis did not change in comparison with baseline and there were no differences between groups.

Duration of artificial ventilation was 360 (326) min in group 1 and 245 (317) min in group 2 ($P = 0.55$). Duration of hospital stay was 12.5 (8) days in group 1 and 14.8 (9.3) days in group 2 ($P = 0.66$). Major adverse events were seen in three patients in group 1 and in two patients in group 2. Adverse events included hyperbilirubinaemia (caused by stenosis of the hepatic duct which required operative revision) and increased serum amylase without clinical pancreatitis in group 1, and atelectasis and hepatic insufficiency (on postoperative day 4 after right hemihepatectomy in a patient with a fatty liver who underwent chemotherapy 4 weeks before operation) in group 2. No adverse event was considered to be associated with donation of HES or HBOC-201. With the exception of the one patient who died of multi-organ failure after hepatic insufficiency 4 weeks after operation, all patients were in excellent condition at the follow-up examination.

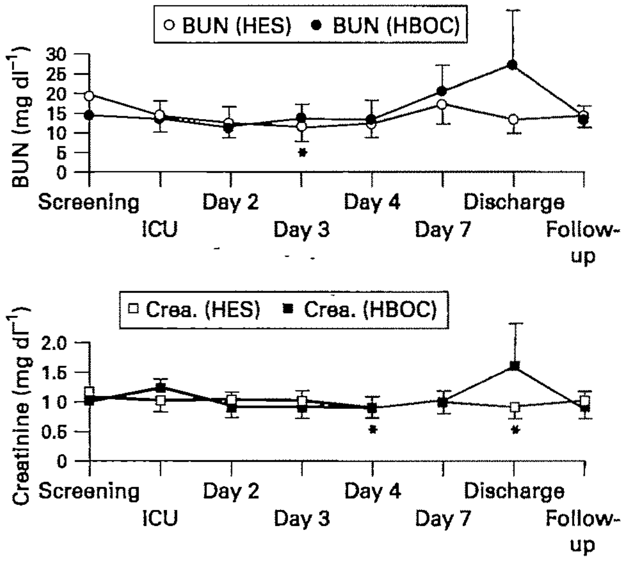

Figure 4 Changes in concentrations of blood urea nitrogen (BUN) and creatinine (Crea.) after preoperative haemodilution with HES or HBOC-201 in liver resection patients. Values are mean (SEM). $*P < 0.05$ *vs* screening.

Discussion

We have shown that a chemically modified ultrapurified bovine haemoglobin administered during preoperative haemodilution was tolerated well in patients undergoing liver resection surgery. However, the study failed to show any advantage of HBOC-201 compared with HES in terms of a sparing effect of allogeneic blood administration in these patients undergoing major abdominal surgery. One explanation for this result is the relatively small dose of HBOC-201, which appears to be too low for perioperative blood substitution in cases of massive blood loss. As the intravascular half-life of haemoglobin appears to be dependent not only on stabilization of the tetramer[10 11] but also on the dose of the haemoglobin solution given,[12] a single dose of HBOC-201 0.4 g kg^{-1} might have resulted in a shorter intravascular life in this study than has been reported in a dose-escalating study with this material.[5] In addition, intraoperative blood loss and perioperative infusions may have diluted the intravascular concentration of bovine haemoglobin. Disappearance into the interstitial and lymphatic space via diffusion has also been reported for intra-molecularly stabilized haemoglobin tetramers.[13] However, the intermolecular stabilization of HBOC-201 with glutaraldehyde resulted in haemoglobin polymers with a molecular size of 64 000–500 000 Da, which is greater than with intra-molecular haemoglobin stabilization and should preclude rapid excretion of this material into the interstitium.

As no free haemoglobin could be detected in urine over time, there is evidence that HBOC-201 was cleared by the reticuloendothelial system (RES). Animal studies have shown that either intra- or intermolecular stabilization of haemoglobin tetramers prevents rapid renal elimination.[14-16] However, a high molecular weight provided by polymerization may enhance uptake into the RES.[17] The effect that some of the haemoglobin formulations may have on the RES is unclear at present. Although there are animal data which described immunosuppressive effects when tetrameric human-derived haemoglobin solutions were given in a model of bacteraemia[18] or in combination with endotoxin,[19] there are no clinical data to suggest that immunosuppression occurs in humans. Our patients showed a transient leucocytosis and reticulocytosis after administration of HBOC-201 but bilirubin concentration was not higher compared with patients who received HES. No clinical correlate for immunosuppression, for example fever, delayed wound healing or concomitant infectious diseases, occurred in our study. However, the number of patients in this study was too small to allow conclusions on side effects of HBOC-201 on the immune system.

The early reticulocytosis on day 3 after operation which was observed in patients after administration of bovine haemoglobin may accord with the uptake of the compound by the RES where it possibly contributes to enhanced production of reticulocytes because of an increased iron supply by HBOC-201.[20]

We have shown that administration of a low dose of HBOC-201 had no toxic side effects on the liver, kidney, pancreas or coagulation, even in patients undergoing liver resection who are very sensitive to toxic influences on these respective organs. Liver enzymes increased to an extent which did not differ from values of patients treated with HES. All results were within the range which normally occurs after liver surgery.[21] As animal data have shown that organ toxicity of some haemoglobin solutions may be a function of impurities[22] we did not expect severe side effects on the liver, kidney or coagulation using an ultrapurified haemoglobin preparation. In contrast with an earlier applied stroma-free haemoglobin solution which resulted in impaired renal function as a result of clinically relevant concentrations of endotoxin and phospholipids,[23] endotoxin and phospholipids in HBOC-201 are undetectable.

One common problem with the use of haemoglobin solutions is oxidation of the free oxyhaemoglobin to methaemoglobin which does not contribute to oxygen transport. This may occur *in vitro* during storage and also *in vivo* after infusion. The HBOC-201 solution has a shelf-life of more than 2 yr when stored at room temperature and contains a maximum methaemoglobin concentration of $\leqslant 10\%$ if the bags are not damaged. However, after the material was given to patients, the fraction of methaemoglobin increased slightly in the HBOC-201 group but was still within the physiological range. It is therefore unlikely that this moderate increase in total methaemoglobin fraction is clinically relevant. Even after a dose of HBOC-201 45 g, the methaemoglobin concentration did not exceed 1.8% in volunteers.[24] HBOC-201 in the oxy-state possesses a very low oxygen affinity which is regulated by chloride ions and not by 2,3-DPG [25] and has been demonstrated to provide adequate tissue oxygen tensions in a model of nearly complete blood exchange.[26] In addition, plasma oxygen transport by HBOC-201 was able to normalize reduced post-stenotic skeletal muscle tissue oxygenation.[27]

The increased oxygen off-loading capacity is a primary property of HBOC-201 and is associated with compensatory haemodynamic changes in order to maintain normal tissue oxygen tensions.[28] Haemoglobin solutions have also been described as having a vasoconstrictive effect as a result of binding of nitric oxide,[29] [30] manifested by increased systemic vascular resistance and possibly by reduced blood flow to specific organs.[31] However, animal data indicate that autoregulatory mechanisms can override vasoconstriction *in vitro*, for example on coronary arteries.[32] In a rat model, Gulati, Sharma and Burhop[33] showed that chemically modified (e.g. diaspirin cross-linked) haemoglobin did not alter organ blood flow.

Vasoconstriction with increased mean arterial pressure (MAP) and decreased cardiac output has been demonstrated in patients undergoing preoperative haemodilution with HBOC-201 before vascular surgery.[34] This is consistent with our findings of an increased MAP on admission of patients to the ICU. Although there is no evidence that the vasoconstrictive effect of haemoglobin solutions is dose dependent,[35] no haemodynamic differences were seen in this study on day 2 after operation or later.

It is unclear if haemoglobin solutions also increase gastrointestinal smooth muscle tone. However, there was no evidence of an increased incidence of gastrointestinal adverse events or increased pancreatic sphincter tone in the HBOC-201 group as pancreatic amylase and alkaline phosphatase were not higher than values in HES-treated patients.

All major complications were considered not be associated with either HES or HBOC-201. It is known from the literature that liver resection carries a high rate of postoperative complications.[36]

Although all haemoglobin formulations are composed of modified haemoglobin with some immunogenic potential, administration of HBOC-201 was not associated with allergic reactions. However, the study of Hertzman, Keipert and Chang[37] revealed antigenic properties of polyhaemoglobin while other animal studies suggested low antigenicity of purified and chemically modified haemoglobin.[38–40]

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Blood salvage during Caesarean section

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Summary

The aim of this study was to assess blood salvage during Caesarean section. In 15 Caesarean sections, red cells lost were collected and washed with a Dideco machine and tested for the presence of fetoplacental material, bacterial contamination, free haemoglobin and fetal blood cells. Successive patients were allocated randomly to one of two groups. In group 1 (n = 34), intraoperative blood was salvaged, while group 2 served as a control. The mean amount of blood salvaged in group 1 was 363 (SD 153) ml. Blood was salvaged following these guidelines: identification of blood group of the mother and fetus; avoidance of aspirating blood from the umbilical cord; commencement of salvage after removing the fetoplacental unit; completely filling the centrifugation bowl with red cells; washing the cells using at least 1000 ml of physiological solution per bowl; and mixing the contents of the bowl, completely eliminating the buffy coat where fetal cells are located. In group 1, the use of homologous blood transfusions was significantly lower (one of 34 (2.9%) patients compared with eight of 34 (23.5%); $P = 0.01$), haemoglobin concentrations during the first 4 days after operation were significantly higher and postoperative hospital stay was significantly shorter. Duration of hospital stay was significantly shorter in group 1 (5.3 (1.9) *vs* 7.3 (4) days; $P = 0.003$). Mean base haemoglobin concentrations were significantly lower in group 1 (10.7 (1.4) *vs* 11.7 (1.5) g dl^{-1}; $P > 0.0001$), while after surgery mean haemoglobin concentrations were significantly higher approximately 3 h after operation compared with the control group (10.2 (1.5) *vs* 8.6 (1.2) g dl^{-1}; $P < 0.0001$). On the first day, haemoglobin concentrations were 9.8 (1.5) *vs* 8 (1.4) g dl^{-1} ($P < 0.0001$), on the second day 9.8 (1.4) *vs* 7.7 (1.4) g dl^{-1} ($P < 0.0001$), on the third day 10.1 (1.5) *vs* 7.5 (1.3) g dl^{-1} ($P < 0.0001$) and on the fourth day 10.4 (1.5) *vs* 8.1 (1.4) g dl^{-1} ($P < 0.0001$). (*Br. J. Anaesth.* 1998; **80**: 195–198)

Keywords: surgery, obstetric; blood, transfusion; blood, replacement; blood, salvage

Counselling of pregnant women on the possibility of autologous blood donation before delivery to avoid any risk to the fetus is unusual.[1] Long-term freezing of autologous blood is possible, but this is not readily available for every pregnant woman. Thus in selected patients undergoing Caesarean section, it may be useful to ascertain the possibility of re-infusing intraoperatively salvaged blood, providing there is evidence that recovered red cells are devoid of contaminants, and major antigenic incompatibilities are avoided (AB0, Rh, Kell). Some studies have been reported: in 1989 a French group described blood salvage in 15 patients undergoing Caesarean section using the Hemonetics "Cell Saver 4" which washes cells without mixing the contents of the bowl.[2] The results showed that: free Hb increased by 20-fold; cultures for *Epidermis staphylococcus* were positive; fetal red cells were present in 20% of cases; and fetal lanugo and scales were found in one case.

Between 1989 and 1991 at Buon Samaritano Hospital, San Jose (CA, USA), four patients giving birth received a total of 9 u. of washed and salvaged blood without amniotic embolism or other complications attributed to re-infusion.[3]

The aim of this study was to assess blood salvage during Caesarean section and the effect of this procedure on perioperative haemoglobin concentrations and postoperative hospital stay.

Patients and methods

All patients gave written informed consent to the study which was approved by the Ethics Committee of the hospital. We studied 68 patients, mean age 32.7 (16–43) yr, body weight 72.5 (SD 11.6) kg and height 160.4 (5.7) cm who were allocated randomly to one of two groups. In group 1 (n = 34) mean age was 33.6 (22–43) yr, body weight 73.3 (SD 12.8) kg, height 161 (SD 5.9) cm, and blood lost during surgery was re-infused. In 17 cases of maternofetal blood group incompatibility, blood was re-infused after ensuring that no fetal blood was present. In group 2 (n = 34), mean age was 31.9 (16–41) yr, body weight 71.6 (SD 10.5) kg, height 160 (5.5) cm, and intraoperative blood loss was not salvaged.

In 43 patients the anaesthetic technique used was combined spinal extradural anaesthesia (elective surgery; 22 patients in group 1), in 12 spinal (urgent; six patients in group 1) and in 13 general anaesthesia (six patients in group 1; extremely urgent).

Blood was salvaged using the Dideco machine (Mirandola, Modena, Italy) which provides good

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Table 1 Indications for Caesarean section (CS) in the two groups

Indication for CS	All patients	Blood salvage	No blood salvage
Fetal distress	11	2	9
Fetal malposition	11	3	8
Repeat CS	23	14	9
Small pelvis	3	1	2
Multiple pregnancy	8	7	1
Elderly primipara	4	2	2
Preclampsia	4	2	2
Placenta praevia	4	3	1

Table 2 Coexisting diseases in the two groups

Co-existing diseases	All patients	Blood salvage	No blood salvage
Uterine fibromatosis	5	5	
Anaemia (Hb <10 g dl^{-1})	4	3	1
Coagulation disorder	2	2	
Respiratory failure	1	1	
Systemic hypertension (>180/100 mmHg)	1	1	
Liver dysfunction	2	1	1
Placental detachment	3	2	1

quality washing because red blood cells can be mixed in the bowl during washing.[4 6] In order to limit contamination, blood salvage was started after extraction of the fetoplacental unit (i.e. during the most "bloody" but "cleanest" phase of the operation when the uterine cavity was open with the blood vessels gaping). Blood enters the aspirator where salvaged blood is mixed with anticoagulant solution (ACD formula A) then, through the connection tubes, to a reservoir where is passes through a 40-micron filter.[4] An adjustable speed peristaltic pump discharges anticoagulated blood to the centrifugation bowl where it is washed with isotonic solution and concentrated.[4 5] The best quality wash is obtained by alternating washing the red blood cells with mixing the bowl contents and reducing centrifugation speed to less than 1000 rpm.[4 6]

To assess the quality of these red cells, in 15 patients blood was salvaged, not re-infused, but subjected to a series of quality tests.

(1) Culture and microbiological tests.

(2) Free haemoglobin in supernatant blood using the Technycon Bayer H2 optic laser globule counter and a photometric method.[7]

(3) Evaluation of fetal haemoglobin with the HPLC DIAMAT (Biorad) automatic system (20 µl of haemolysed blood were introduced in the cationic exchange silica gel chromatographic column which separates haemoglobin by tampons with progressively increasing ionic strength and pH, enabling elution of haemoglobin by the column at a precise, standard time). Fetal haemoglobin elutes at 3.5 min and a filtered photometer reads the fractions eluted at 415 and 690 nm and a computer performs the integration of the chromatogram peaks.[8 9]

(4) Microscopic slide examination of blood salvaged and washed, and stained using the May–Grunwald–Giemsa method.

(5) Assessment of procoagulant activity of placental origin in the supernatant from salvaged and washed blood. The whole of each sample was tested after microfiltration (this liquid was added in equal parts to a pool of normal plasma). The results were compared with those obtained by adding, in the same proportion, tampon PBS pH 7.4 to the pool of normal plasma. Three different tests were: addition of $CaCl_2$ 0.025 mol litre^{-1}, addition of kaolin 5 g litre^{-1} and addition of APTT reagent diluted 1:50 (containing homogenized human platelets and kaolin).

(6) Fetal red blood cell contamination evaluated by cytofluorimetry for fetomaternal incompatibility (ABO, Rh). In these cases, fetal haemoglobin was not determined.

(7) Assessment of blood groups. EDTA-containing samples from mother and umbilical cord (fetus) were analysed immediately after delivery for A, A1, B, D, C, c, E, e, K and k antigens using standard methods (Kell-incompatibilities were not found).

(8) Evaluation of the presence of fetal red blood cells in salvaged blood in case of ABO or Rh incompatibility, or both. Erythrocyte antigen expression was studied by immunofluorescence and flow cytometry[10–13] and different polyclonal antisera were used, according to the fetal antigenic mosaic.[14]

In 17 patients with ABO incompatibilities, we used hyperimmune anti-A and anti-B antisera with an IgG titre >1:512 diluted appropriately in saline; in patients with Rh incompatibility, the following reagents were used: anti-D (Ortho Diagnostic System, Raritan NJ, USA) and anti-D, anti-C, anti-c anti-E and anti-e (A. Menarini Diagnostici, Firenze, Italy). All antisera were approved for slides and test tubes. Fluorescein–isothiocyanate conjugated rabbit anti-human IgG immunoglobulins were used as a second-step reagent.

A standard immunofluorescence technique was used, as described previously. The fluorescence intensity of each sample was evaluated using a Coulter EPICS XL-MCL cytofluorimeter (Coulter, Hialeah, FL), equipped with a 488 mm air-cooled argon laser. An electronic bit-map gating for red blood cells was set by combining forward scattering (log scale) with 900 light scattering (linear scale) and the percentage of positive erythrocytes was evaluated both by histograms with log-integrated green fluorescence, plotted against the number of red cells counted (10 000 at least) and by plotting green fluorescence analysis against forward scattering. Histograms and MCV values were generated by the standard software of the EPICS XL MCL-dedicated computer.

Indications for Caesarean section, co-existing diseases, perioperative haemoglobin concentrations, intra- and postoperative complications, and duration of hospital stay were recorded for all patients (tables 1, 2). Statistical analysis was carried out using contingency table tests, Fisher's test, ANOVA and the Mann–Whitney test.

Results

Our quality tests on salvaged blood revealed that: the culture and microbiological tests were negative; fetal haemoglobin was absent, except in three patients in which it was 1.8–2.0%. In these three patients fetal haemoglobin was also present in maternal blood (1.5–1.8%) which confirms transplacental passage of fetal haemoglobin during pregnancy; free haemoglobin was virtually absent (mean 0.05 (SD 0.06) mg %); fetoplacental material was not observed on

Table 3 Use of homologous red blood cells (HRBC) and duration of postoperative hospital stay (number (%) or mean (SD) [range]) in both groups

	All patients	Blood salvage	No blood salvage	ANOVA
No HRBC patients	59 (86.7%)	33 (97%)	26 (76.5%)	
HRBC patients	9 (14%)	1 (2.9%)	8 (23.5%)	P =0.0001
Postop. hospitalization (days)	6 (2.9)	5.3 (1.9) [3–12]	7.3 (4) [5–21]	P=0.003

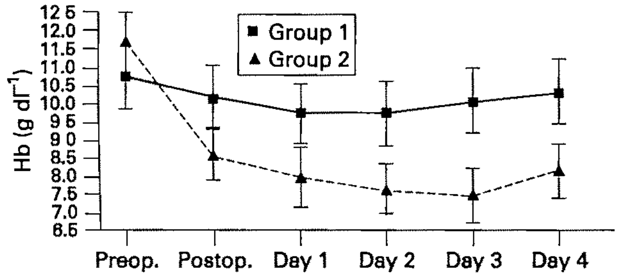

Figure 1 Changes in haemoglobin (Hb) concentration in the two groups. Postop. = 6 h after surgery.

microscopy. Leucocytes and cell fragments were detected only in cases where the buffy coat had not been eliminated completely; and study of procoagulant activity in salvaged blood revealed a normal recalcification time in 13 of 15 patients. In two samples, where during salvage the buffy coat was not removed totally because of incomplete filling of the bowl, recalcification time was shortened (compared with the pool and tampon). This shortening was eliminated by removing the fragments of lysed cells (red cells, white cells, amniotic cells) and filtration of the supernatant.

The presence of fetal blood, tested by cytofluorimetry in all cases with maternofetal blood group incompatibility, was found in a quantity of 0.8–1.4% in four patients who did not receive re-infusion of blood. The cause of this contamination was errors in carrying out the salvage procedure, such as aspiration of blood from the umbilical cord and incomplete removal of the buffy coat in the washing technique produced by incomplete filling of the bowl.

The two groups were similar in age, height and body weight. The mean amount of blood salvaged in the 34 patients who underwent re-infusion was 363 (SD 153) (range 125–800) ml. Mean packed cell volume of re-infused red blood cells was 62 (SD 5) %. Five days after surgery, one of these patients received transfusion of 2 u. of homologous blood because of persistent anaemia (with symptoms of dizziness on assuming an upright position). In the second group, eight patients received homologous blood transfusions between the first and fifth day. The use of homologous transfusions (table 3) was significantly different in the two groups (contingency tables with Fisher's test, $P = 0.01$).

In patients in whom blood salvage was carried out, mean basal haemoglobin concentrations were significantly lower than those in group 2 patients (ANOVA, $P = 0.001$), while mean postoperative haemoglobin concentrations 3 h after surgery, on day 1, 2, 3 and 4 after operation were significantly higher (ANOVA, $P < 0.0001$) (fig. 1).

Postoperative complications in group 1 included cystitis with pyrexia (one patient) and subfascial parietal haematoma (one patient). In group 2, complications included hyperpyrexia after transfusion of homologous blood following persistent mild fever and discharge against the doctor's advice (two patients), and pulmonary oedema and ascites needing intensive care for 4 days (one patient). There were no complications as a result of re-infusion of salvaged blood cells.

With regard to postoperative hospital stay (table 3) because the SD value in the two groups differed considerably, ANOVA could not be used, and therefore the mean rates of the Mann–Whitney tests were used. This test revealed that hospital stay was significantly shorter ($P = 0.003$) in group 1.

Discussion

We have demonstrated that in the absence of contaminants and antigenic incompatibilities caused by fetal red blood cells, salvaged blood was re-infused safely.

The increasing use of surgery in childbirth and the subsequent need for blood transfusion, together with patients' reluctance to receive homologous blood transfusions, is posing problems for the anaesthetist. Predepositing blood is still experimental and not performed routinely in obstetric surgery for several reasons: (1) fear of removing excess amounts of blood because of possible repercussions on uterine and fetal activity, as reported in the literature[1]; (2) varying degrees of anaemia in at least 50% of cases; (3) difficulty in predicting the date of childbirth, even by surgical intervention (planned Caesarean section brought forward because of concerns regarding fetal wellbeing); and (4) limited usefulness in patients with severe haemorrhage.

Acute preoperative isovolaemic haemodilution is difficult to perform because of the physiological haemodilution present in the pregnant patient. We observed a higher postoperative haemoglobin concentration in patients who underwent intraoperative salvage and this confirms the findings of Orr and Blenko,[15] who reported a higher osmotic resistance than homologous banked blood cells, and McShane and colleagues,[16] who observed a higher concentration of 2,3 diphosphoglycerate, a more physiological concentration of potassium and pH, and a higher content of haemoglobin in blood washed with the Dideco Autotrans BT 795 compared with donated blood. Later, Alleva and colleagues[17] reported less damage to red cells salvaged during operation with the Dideco STAT and cells recovered after operation with the Dideco BT 797 Recovery compared with cells predeposited in SAG-M and preserved in the refrigerator for 21 days at 4 °C. We conclude that blood salvage may be useful to avoid autologous blood transfusion and it may be associated with a better outcome and shorter hospital stay.

Blood salvage during Caesarean section may be performed according to these guidelines: determine the blood group of the mother and fetus; avoid aspiration of blood from the umbilical cord; start salvage after removing the fetoplacental unit; completely fill the centrifugation bowl with red cells; wash the cells accurately using at least 1000 ml of physiological solution per bowl; and mix the contents of the bowl completely to eliminate the buffy coat where fetal cells are located

By following these guidelines we have obtained salvaged blood without fetal red cells or with minimal contamination of fetal elements, which may be re-infused even when maternofetal blood groups are incompatible.

If a pregnant woman is transfused with homologous blood at the end of delivery there is a risk of receiving incompatible Fy and Jk antigens. The highest estimated contamination of fetal blood, if present, in our procedure should be about 3 ml, which is in the range of spontaneous fetomaternal haemorrhage.[14] Thus in our study the risk of alloimmunization from the presence of fetal red cells in salvaged blood is as likely as in a normal delivery and problems caused by administration of homologous blood is avoided. Moreover, where fetomaternal D-antigen incompatibility exists, giving the patient Rh immune globulin (300 μg) may prevent sensitization to 15 ml of packed D positive red blood cells.

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Prevention of spinal anaesthesia-induced hypotension in the elderly: i.m. methoxamine or combined hetastarch and crystalloid

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Summary

We have compared two methods of reducing hypotension during spinal anaesthesia in elderly patients, 6% hetastarch and crystalloid or methoxamine 10 mg i.m., in terms of haemodynamic stability and requirements for additional vasopressors. Sixty-two patients (aged 60–97 yr) undergoing surgical fixation of fractured neck of femur were allocated randomly to receive 6% hetastarch (Hespan) 500 ml followed by Hartmann's solution 500 ml (group HS, $n = 32$) or a bolus injection of methoxamine 10 mg i.m. (group MX, $n = 30$), 10 min before induction of spinal anaesthesia with 0.5% hyperbaric bupivacaine 2.25–3.0 ml. Arterial pressure was measured non-invasively by an oscillotonometer at 2-min intervals from 0 to 40 min and at 5-min intervals thereafter. Methoxamine 2 mg i.v. was given if systolic arterial pressure (SAP) decreased to <100 mm Hg. Hypotension was defined as a 25% decrease from baseline SAP or mean arterial pressure (MAP). Patient data, sensory level and blood loss were similar in the two groups. SAP and MAP increased initially from baseline until induction of spinal anaesthesia and then decreased for 30 min in both groups, but remained higher in group MX ($P < 0.05$). Heart rate (HR) decreased from baseline in group MX ($P < 0.05$) and was less than in group HS at all times from 2 to 60 min ($P < 0.01$). The incidence of SAP hypotension (47% *vs* 75%; $P = 0.03$, odds ratio (OR) = 3.43) and MAP hypotension (47% *vs* 67%; $P = 0.09$, OR = 2.51) was less in group MX than in group HS. Requirements for rescue methoxamine i.v. (27% *vs* 53%, $P = 0.04$, OR = 3.11) was less in group MX than in group HS but the dose of rescue methoxamine given (mean 6.3 (95% confidence intervals 3.0–9.6) *vs* 8.9 (5.6–12.2) mg) and time to onset of hypotension (20.7 (14.5–26.7) *vs* 17.3 (11.4–23.1) min) were similar in groups MX and HS, respectively. We conclude that methoxamine 10 mg i.m., given 10 min before induction of spinal anaesthesia in normovolaemic elderly patients, reduced subsequent SAP and MAP hypotension, HR and requirements for rescue vasopressor therapy compared with a combination of 6% hetastarch 500 ml and crystalloid 500 ml. The previously reported benefit of such volume administration may not extend to the elderly. (*Br. J. Anaesth.* 1998; **80**: 199–203)

Keywords: anaesthesia, subarachnoid; complications, hypotension; fluids, i.v.; fluid therapy; sympathetic nervous system, methoxamine.

Systemic hypotension is the most common complication of spinal anaesthesia, with an incidence of 25–82% in the elderly.[1–3] Despite no prospective outcome data, it seems reasonable to be concerned that the elderly may be at increased risk of long-term complications from hypotension occurring during spinal anaesthesia, because of reduced physiological reserve and atherosclerosis, particularly coronary artery disease.[3] A retrospective study suggested that patients who became hypotensive during anaesthesia had a five-fold increased risk of perioperative myocardial infarction compared with patients who did not develop hypotension.[4]

Strategies for treating spinal anaesthesia-induced hypotension include i.v. volume administration, which increases circulating volume and cardiac output in an effort to compensate for the expansion of the capacitance vessels, or pharmacological reversal of the reduction in systemic vascular resistance which inevitably accompanies spinal anaesthesia, using vasopressor agents.[5]

The practice of volume loading, that is rapid infusion of crystalloids before induction of spinal anaesthesia, dates from 30 yr ago, in which such infusions apparently reduced the high incidence of hypotension in obstetric patients.[6 7] More recent work from this decade has cast doubt on the efficacy and benefit of this practice. Several studies in women undergoing spinal anaesthesia for Caesarean section or tubal ligation have found that volume administration produces marginal, if any, reduction in the incidence of hypotension[8–10] while also causing significant increases in central venous pressure, pulmonary oedema and haemodilution, which may potentially have detrimental consequences.[10–12] In a recent investigation comparing crystalloid, gelatin colloid and no volume administration for spinal anaesthesia in an elderly population, we found that withholding of fluids was not associated with any greater incidence of hypotension or ephedrine use than the use of either crystalloid or colloid volume administration.[13]

However, volume administration with a combination of 6% hetastarch as synthetic colloid and crystalloid, in equal proportions, has been shown to

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produce significantly less hypotension than an equal volume of crystalloid or colloid alone in parturients.[11] [12] Whether this regimen would be effective in the elderly is unknown. Hetastarch 6% in 0.9% saline is a synthetic colloid derived from amylopectin, with a molecular weight of 450 000. Its pH is 5.5, osmolarity 310 mosmol litre^{-1} and its intravascular half-life is 25 h. Anaphylactoid reactions are less frequent than with other synthetic colloids, but it is expensive (approximately £30 per 500 ml compared with £0.65 for 1 litre of crystalloid) and may induce coagulopathy.[14] [15]

The alternative strategy for management of spinal anaesthesia-induced hypotension is the use of vasopressor agents, of which the most popular is ephedrine, a combined alpha and beta adrenergic agonist. However, the unreliability of its vasoconstrictive efficacy and its tendency to cause a positive chronotrophic effect on the heart have raised doubts about its safety in elderly patients.[16] [17] It makes physiological sense to use an alpha adrenergic agonist, such as methoxamine, which would pharmacologically reverse undesirable peripheral vascular dilatation, maintaining systemic arterial pressure, while avoiding unwanted cardiac effects. Metaraminol is the only commonly used pure alpha adrenergic agonist that has been investigated specifically during spinal anaesthesia in an elderly population.[18] These agents may be given by continuous infusion, but this requires an infusion pump, which may be too cumbersome for routine use, and has the potential for hazardous errors in its administration.

In this study, we have evaluated the incidence and onset time of hypotension and need for further vasopressor therapy in an elderly population given one of two prophylactic measures designed to minimize spinal anaesthesia-induced hypotension: methoxamine 10 mg i.m. or a 1-litre volume administration regimen comprising 6% hetastarch 500 ml and Hartmann's solution 500 ml.

Patients and methods

After obtaining Institutional Ethics Committee approval and informed consent, we studied 65 ASA I, II or III patients (aged 60–96 yr) undergoing emergency hip surgery (insertion of Austin–Moore prosthesis or dynamic hip screw). Exclusion criteria were ASA IV or V patients, uncontrolled hypertension (i.e. SAP >160 mm Hg) or congestive cardiac failure, clinical evidence of significant dehydration (reduced skin turgor, dry mucous membranes, systolic arterial pressure <100 mm Hg, Na^+ > 145 mmol litre^{-1}, urea >10 mmol litre^{-1}), those aged less than 60 yr and those for whom spinal anaesthesia was contraindicated. Patients were not premedicated, but all received continuous infusion of crystalloid as maintenance fluids (1.5 ml kg^{-1} h^{-1}).

On arrival in the induction room all patients were met by an anaesthetist other than the one who would be in charge of induction and monitoring of anaesthesia. Having confirmed their hydration status clinically, and noted the duration of fasting from oral fluids together with preoperative Na^+ and urea values, a 16-French gauge peripheral cannula was inserted. Patients were allocated randomly, using a sealed, sequentially numbered, envelope technique, to one of two groups: group HS received 6% hetastarch 500 ml (Hespan) followed by crystalloid (Hartmann's solution) 500 ml over 10–15 min while the patient was positioned and prepared for spinal anaesthesia; group MX received methoxamine 10 mg by deep gluteal i.m. injection after being positioned for spinal anaesthesia. Maintenance fluid (1.5 ml kg^{-1} h^{-1}) using crystalloid (Hartmann's solution) was infused continuously in all patients.

Spinal anaesthesia was induced in all cases in the lateral position, the operative side inferior, at L2–3 or L3–4, using 0.5% hyperbaric bupivacaine 2.25–3.0 ml (Marcain; Astra Pharmaceuticals), with a 22-gauge spinal needle, injected over 15–20 s under aseptic conditions by an anaesthetist other than the one who had administered the preventive strategies described above and who was therefore unaware of the study groups. This physician also managed the patient during anaesthesia and noted the haemodynamic data. The volume of bupivacaine used was left to this anaesthetist, depending on the patient's weight, height, sex and physical condition. Patients were kept in the lateral position for another 5 min to ensure they were pain free before transfer to the position for surgery. Sensory level was determined bilaterally at 15 min using pinprick.

Systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures were measured by automated, non-invasive oscillotonometry (Dinamap, Datex Cardiocap II, Helsinki, Finland) on three successive occasions on arrival in the induction room to establish baseline levels, at 2-min intervals until 30 min after induction of spinal anaesthesia and at 5-min intervals thereafter. Heart rate (HR) was noted from continuous electrocardiography, and pulse oximetry was also monitored throughout spinal anaesthesia and surgery. Hypotension was defined as a 25% decrease from baseline for both SAP and MAP, or an absolute systolic value <100 mm Hg. Rescue therapy for hypotension comprised methoxamine 2–4 mg i.v., repeated at 2-min intervals as necessary. This was given if SAP was <100 mm Hg on two consecutive readings or if indicated on clinical grounds, that is if new pallor was noted or if the patient reported nausea, vomiting or unusual lightheadedness. Blood loss was estimated in the perioperative period by the sum of collected spilt blood and swab weighing. Observations were discontinued after 70 min or immediately after arrival in the recovery room, whichever occurred sooner.

Data were analysed using Statsview II. Mean (95% confidence intervals) values were obtained for normally distributed data and compared using the Student's unpaired *t* test. Repeated measures analysis of variance was used for serial measures of SAP, MAP and HR. Paired Student's *t* test and *post hoc* Bonferroni correction for multiple comparisons were used for comparison of these variables between baseline and sequential times. The Mann–Whitney *U* test was used to compare skewed data. Categorical data were compared with chi-square analysis of contingency tables with Yates' correction or Fisher's exact test where cell values were <5. The power of this study was calculated prospectively as follows: in a previous investigation, we found an incidence of spinal-induced hypotension in the elderly of 50%,[11] consistent with other studies. The minimum clinically

Table 1 Patient and spinal block characteristics (mean (95% confidence interval) or number). No significant differences

	Group HS (n=32)	Group MX (n=30)
Age (yr)	78.1 (60–93)	78.0 (60–96)
Sex (M/F)	9/23	11/19
Height (cm)	162 (156–165)	163 (160–170)
Weight (kg)	64.4 (59.2–69.7)	64.1 (58.8–69.4)
Fasting time (h)	12.4 (11.3–13.6)	11.9 (10.9–12.8)
Na^+ (mmol $litre^{-1}$)	134.5 (131–138)	136.1 (134–138)
Urea (mmol $litre^{-1}$)	7.1 (6.2–8.0)	6.6 (5.8–7.3)
ASA (I:II:III) (n)	6:14:12	8:15:7
Block level	T7 (T2–12)	6 (T2–12)
High block (n) (T8 or higher)	16	17
Blood loss (ml)	217 (220–413)	196 (134–258)
Time to hypotension (min)	17.2 (11.4–23.1)	20.7 (14.5–26.7)

important difference we wished to detect was a 30% difference in the proportion of patients developing hypotension (e.g. 65% *vs* 35%), assuming equal patient groups. Thus this study had 75% power to detect these differences at P = 0.05 and n = 30 in each group.

Results

Although 65 patients were enrolled in the study, two (one in each group) were subsequently lost because of failure to establish spinal anaesthesia, and another (group MX) had inadequate subarachnoid block, all three requiring general anaesthesia. Hence, data from 62 patients were analysed; n = 32 in group HS and n = 30 in group MX.

The groups were similar in age, sex, characteristics, preoperative Na^+ and urea values, and preoperative fasting time. Blood loss was not significantly different between groups (table 1). Median time to induction of spinal anaesthesia after commencement of therapy (volume administration or methoxamine i.m.) was 10.2 (range 8–13) min. Sensory level at 15 min and proportion of patients with a high block (defined as T8 or higher) were also similar in each group, and the overall proportion of patients with a high block was 53%. Mean time to onset of hypotension was 17.2 min in group HS and 20.7 min in group MX (ns) (table 1).

The incidence of SAP hypotension was 75% in group HS compared with 47% in group MX (P = 0.03, odds ratio (OR) = 3.43; 95% confidence interval (CI) for this 28% difference in the proportion of patients developing SAP hypotension was 4.7–51.3%). Similarly, 67% of patients in group HS compared with 47% in group MX demonstrated MAP hypotension (P = 0.09, OR = 2.51). The incidence of rescue methoxamine therapy was 38.5% (53% for group HS *vs* 27% for group MX; P = 0.04, OR = 3.11). However, in those patients given methoxamine, the mean dose was not significantly different between groups (8.9 (95% CI 5.6–12.2) *vs* 6.3 (3.0–9.6) mg) (table 2).

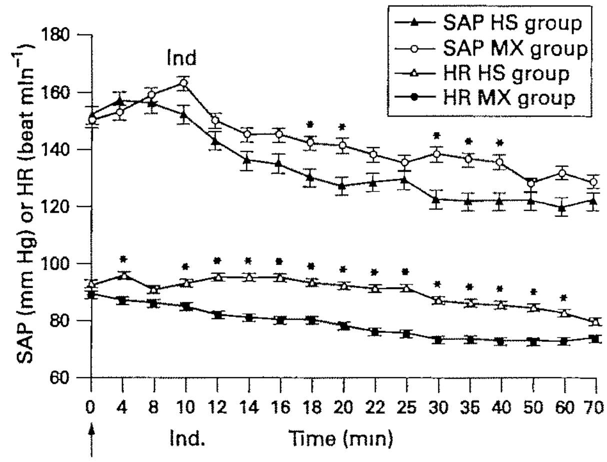

Figure 1 Mean (SEM) systolic arterial pressure (SAP) and heart rate (HR) in groups HS and MX. Ind. = Induction of spinal anaesthesia; arrow indicates time of volume administration or administration of methoxamine i.m. $*P < 0.05$.

Absolute SAP and MAP increased in both groups after commencement of therapy and before spinal anaesthesia, but the difference between groups was not significant (fig.1). HR remained unchanged in group HS but decreased significantly from baseline in group MX and remained significantly lower in group MX than in group HS at all times (fig. 1). After induction of spinal anaesthesia, SAP and MAP decreased significantly in each group with respect to baseline, but absolute values of SAP and MAP were consistently higher in group MX up to 60 min after induction of spinal anaesthesia, reaching statistical significance at the times shown (figs 1, 2). Diastolic arterial pressure in groups HS and MX were: baseline 81.3 (95% CI 75–86) *vs* 79.2 (73–85) mm Hg, at 8 minutes after methoxamine or volume administration 67 (61–73) *vs* 75 (71–80) mm Hg (P < 0.05) and at 20 min after induction of spinal anaesthesia, 64 (59–70) *vs* 71 (65–79) mm Hg (P < 0.05). There were no significant differences between groups in diastolic arterial pressure at any other time.

Discussion

Spinal anaesthesia blocks efferent sympathetic fibres and reduces systemic vascular resistance by decreasing the sympathetic tone of the arterial circulation. There is also peripheral venous pooling of blood, which may reduce cardiac output.[5 19] Such changes frequently cause systemic hypotension, which may be harmful in the elderly with incipient cardiac and renal failure. However, baroreceptor-mediated compensatory cardiovascular responses result which tend to maintain arterial pressure.[19] Should the sensory level extend to T8, release of catecholamines by the

Table 2 Incidence of hypotension and requirements for rescue methoxamine i.v. in the two groups. SAP = Systolic arterial pressure, MAP = Mean arterial pressure. * Chi-square statistical analysis except Mann-Whitney U test

	Group HS (n=32)	Group MX (n=30)	P
Incidence of SAP hypotension (n (%))	24 (75)	14 (47)	0.03
Incidence of MAP hypotension (n (%))	22 (68)	14 (47)	0.08
Methoxamine requirements (n (%))	17 (53)	8 (27)	0.04
Methoxamine dose (mean (95% CI))	8.9 (5.6–12.2)	6.3 (3.0–9.0)	0.3*

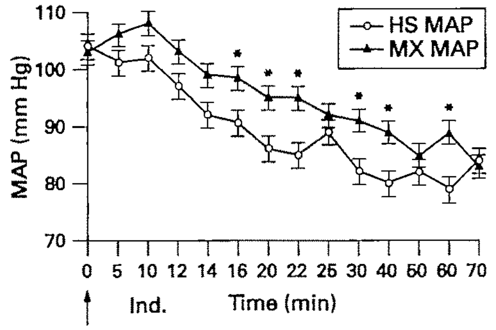

Figure 2 Mean (SEM) mean arterial pressure (MAP) in groups HS and MX. Ind. = Induction of spinal anaesthesia, arrow indicates time of volume administration or administration of methoxamine i.m. *$P < 0.05$.

adrenal gland is compromised and if it reaches T1, all cardiac compensation potential is lost.[5]

Our comparison of two measures intended to reduce hypotension in elderly patients showed greater haemodynamic stability with pre-emptive methoxamine 10 mg i.m. given 10 min before spinal anaesthesia compared with an infusion of 6% hetastarch and crystalloid, in contrast with recent studies in parturients[11 12] and in non-pregnant young women, which found fluid administration of apparent benefit.[23] This may reflect the fact that we used a total volume of 1 litre (6% hetastarch 500 ml and crystalloid 500 ml) compared with 1.5 litre[13 20] and 2 litre.[12] Elderly patients with hip fractures are particularly susceptible to hypotension during spinal anaesthesia because they may be hypovolaemic from blood loss into the fractured joint and have a high incidence of co-existing disease. However, we believe that rapid infusion of up to 2 litre of fluid would possibly result in haemodynamic embarrassment from circulatory overload.

We propose that colloid solution would be more effective in preventing spinal-induced hypotension, as its large molecular weight ensures it remains in the plasma body fluid compartment. None the less, a recent study with large numbers of patients ($n = 85$) comparing crystalloid, gelatin colloid and no fluid treatment in patients aged more than 60 yr found no significant difference in the incidence of hypotension or requirements for rescue vasopressor therapy.[13] Intravascular fluids *per se* do not reverse decreases in systemic vascular resistance, rather they may increase cardiac output.[3 5 21] A more plausible explanation for the failure of this combined fluid administration regimen in the elderly may be that the reduced physiological reserve of older patients may make them less able to respond to volume with a corresponding increase in cardiac output.[3 17] Moreover, 75% of any crystalloid infused rapidly diffuses into the interstitium, where it cannot be as effective as a volume expander.[22] Furthermore, infused fluid (with either crystalloid alone or in combination with hetastarch) stimulates atrial natriuretic peptide (ANP) secretion in women undergoing spinal anaesthesia for Caesarean section,[23] tending to decrease systemic vascular resistance and initiate diuresis. If this were also true in elderly patients, it may explain the ineffectiveness of fluid administration in preventing hypotension.

Ephedrine, a combined alpha and beta agonist, is the most commonly used vasopressor in the elderly.[3] It may be ineffective in reversing the spinal-induced decrease in SVR, possibly because of its beta effect, causing arteriolar vasodilatation in opposition to its alpha vasoconstrictive effect.[16 17] Moreover, its beta-mediated increase in heart rate exposes elderly patients with latent coronary artery disease to myocardial ischaemia. However, in ASA III patients, many of whom would be in the elderly age range, a combination of prophylactic i.m. and i.v. ephedrine improved haemodynamic stability, albeit with tachycardia.[24 25] In contrast, a pure alpha adrenergic agonist (metaraminol), given as a continuous infusion (0.5–5.0 mg h^{-1}), maintained SAP by increasing SVR and central venous pressure, compared with a similar group of elderly patients receiving synthetic colloid alone. However, one-third of patients receiving the metaraminol infusion developed inadvertent hypertension.[18] The increased SVR was associated with a decrease in heart rate both in this and our present study, presumably because of a baroreceptor-mediated reflex bradycardia. Despite the fact that we did not find inadvertent hypertension after methoxamine, it could be that a prolonged delay or failure to establish spinal anaesthesia would cause inadvertent hypertension.

Our finding of improved haemodynamic stability with methoxamine is the first report of its efficacy in male and female elderly patients undergoing spinal anaesthesia for emergency orthopaedic surgery, and is consistent with the results of another small study ($n = 36$) in which MAP was maintained and blood loss reduced in males undergoing transurethral resection of the prostate, given methoxamine 10 mg i.m., 15 min before induction of spinal anaesthesia.[26] In our study, there was no significant difference in blood loss between those receiving methoxamine and those receiving fluid administration. We chose to study methoxamine i.m. believing this to be a more convenient form of administration and less expensive because an infusion pump is not required. Although we have shown that arterial pressures were better preserved using pre-emptive methoxamine, its effect on cerebral and coronary perfusion remains unknown. Such measurements are beyond the scope of this study and are not widely available in current clinical practice.

Our data may have been adversely affected by some of the design features of this study. Baseline arterial pressure was calculated from the mean of three readings, obtained in the semi-recumbent position immediately on arrival in the induction room when many patients would be quite anxious. Subsequently, readings were obtained in the supine or lateral position of surgery. Non-invasive (Dinamap) recording of arterial pressure is accurate only to within ±10%, but the same machine was used in all patients and invasive arterial pressure measurements are rarely used in our practice in this setting. The fasting time varied from 10 to 15 h but all patients were given i.v. fluids at maintenance rates during this time. It was not practical for one anaesthetist to perform all spinal blocks, thus some variation in technique may have occurred. Sensory level was assessed at 15 min, which may have been too early, even using a hyperbaric solution. It would have been interesting to re-assess sensory level and to continue our observations for another 30–60 min in the recovery room to confirm that haemodynamic values were beginning to stabilize.

There is widespread consensus that normovolaemia must be maintained during spinal anaesthesia, and crystalloid 8 ml kg^{-1} has been suggested by Critchley as an appropriate infusion volume to be given as the block is evolving, that is over the initial 10–20 min. However, use of large pre-emptive infusions over a shorter time span are demonstrably ineffective in preventing spinal-induced hypotension and may be detrimental, especially in the elderly.[3, 5, 11–13, 16–19, 27]

In summary, in this prospective, randomized, double-blind, clinical study, methoxamine 10 mg i.m., given 10 min before spinal anaesthesia, resulted in greater haemodynamic stability in normovolaemic elderly patients undergoing emergency hip surgery compared with i.v. administration of 6% hetastarch 500 ml and crystalloid solution 500 ml. The previously reported benefit of this fluid regimen may not extend to the elderly.

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LABORATORY INVESTIGATIONS

Reduced quality of clot formation with gelatin-based plasma substitutes

S. N. Mardel, F. M. Saunders, H. Allen, G. Menezes, C. M. Edwards, L. Ollerenshaw, D. Baddeley, A. Kennedy and R. M. Ibbotson

Summary

We have studied, over a wide range of dilutions using techniques of clot weight, thrombelastography and scanning electron microscopy, the physical properties of a blood clot formed *in vitro* when fresh blood was diluted with gelatin-based colloid solutions compared with crystalloid controls. The colloid solutions tested (3.5% polygeline (Haemaccel) and 4% succinylated gelatin (Gelofusine)) produced clots that had reduced median weight ($P<0.001$ and $P=0.018$, respectively) and reduced mean shear modulus ($P<0.001$) compared with crystalloid controls. Scanning electron microscopy showed that the fibrin formed a less extensive mesh in the presence of the gelatin-based colloids compared with crystalloid. Reduction in clot quality with gelatin-based colloids has not been noted previously and further work is needed to ascertain if this occurs *in vivo* as these solutions are used frequently in patients who require full haemostatic competence. (*Br. J. Anaesth.* 1998; **80**: 204–207)

Keywords: blood, coagulation; blood, colloids; fluids, i.v.; blood, haemostasis; blood, replacement; measurement techniques, thrombelastography

Plasma substitutes containing degraded and modified gelatin are being used increasingly in pre-hospital, resuscitation, perioperative and intensive care situations. Often they are the fluid of choice in patients with uncontrolled haemorrhage both before blood transfusion and in conjunction with transfusion of packed cells. Unlike the dextran and starch solutions, so far they have been considered as having no significant effect on clotting mechanisms following studies based principally on clotting times.[1–4]

While measuring whole blood coagulation times after *in vitro* dilution with colloids we noted a striking difference in clot quality compared with that seen with dilution using crystalloid. Our preliminary findings have been reported previously.[5] In this article we describe more detailed investigations using clot weights, haematological analysis, thrombelastography and scanning electron microscopy, and include a description of the dose–response effect of varying degrees of dilution using regression analysis.

Materials and methods

Wherever fresh whole blood was used, care was taken to avoid prolonged venous stasis, venepuncture from the same site or delays in pipetting, and experiments were conducted under strict temperature control.

CLOT WEIGHTS

A total of 35 fresh whole blood samples were diluted to 15%, 30%, 45%, 60% and 75% with 0.9% sodium chloride and Ringer's solution (controls) or the test substances, 4% succinylated gelatin (Gelofusine, B. Braun (Medical) Ltd) and 3.5% polygeline solution (Haemaccel, Hoescht UK Ltd). After dividing each sample into test and control, the total volume of each sample after dilution was 5 ml. Clot weights were measured using the method described by Macfarlane.[6] Because the clots would not adhere to a glass rod the test was modified by separating the clot from plasma on gauze in a funnel. Clots were weighed on an electronic balance and then examined physically, both by inspection and by attempted dissection with a blunt probe. The remaining serum was then subjected to the following analyses: red blood cell count, platelet count, fibrinogen (Clauss technique) and D-dimers (Dimertest II, Agen Biomedical Ltd).

THROMBELASTOGRAPHY

Coagulation of 70 samples of fresh whole blood at the same dilutions as above were examined by thrombelastography. Each sample was similarly divided and diluted using the test and control solutions and the paired samples placed into the test cylinders of a thrombelastograph (Hellige GMBH) using the method described by De Nicola.[7] This measures the elasticity of the fibrin network within a clot and records this on a calibrated paper chart. Measurements are not affected by viscosity changes. Maximum amplitude (MA) of the graph is measured in millimetres and from this shear modulus (ε) is calculated using the formula $\varepsilon=(100\times MA)/(100-MA)$,

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Table 1 Clot weights, combining all dilutions (median (interquartile range))

	Haemaccel	Control	Gelofusine	Control
n	20	20	15	15
Clot weight (g)	1.214(0.666–1.521)	1.439(0.848–1.982)	1.104(0.482–1.500)	1.489(1.058–1.677)

Table 2 Clot strength experiments, combining all dilutions

	Haemaccel	Control	Gelofusine	Control
n	35	35	35	35
Mean shear modulus	67.4	91.3	75.1	96.5
95% CI for the paired differences	−28.0 to −19.8		−26.8 to −15.9	

given that the normal value of MA is 50 mm for whole blood, and this corresponds to a modulus of 100.

SCANNING ELECTRON MICROSCOPY

Clots were examined by scanning electron microscopy (SEM) using fresh whole blood diluted to 33% and 66% with 0.9% sodium chloride (control), 3.5% polygeline and 4% succinylated gelatin. An additional control of undiluted blood was also examined. Blood clots were fixed initially with 2.5% glutaraldehyde, buffered with sodium cacodylate 0.1 mol litre^{-1} (pH 7.4) containing $CaCl_2$ 2 mmol litre^{-1} for 2 h, then washed in the same buffer and post-fixed in osmium tetroxide for 1 h. The clots were washed, dissected into smaller pieces in 70% ethanol and stored in the same solution overnight at 4°C. The clots were then dehydrated, critical point dried and sputter-coated with gold.[8] All SEM specimens were examined in a Hitachi S-4500 field emission scanning electron microscope, using an accelerating voltage of 5 kV.

Comparison of differences in weight between the plasma substitutes and their controls was carried out using a Wilcoxon signed rank test; elasticity was compared using paired *t* tests. To investigate the relationship between dilution and elasticity, regression techniques were used. Both linear and quadratic models were fitted to the data to assess the observed relationship.

Results

None of the whole blood dilutions containing gelatin colloids formed a firm plug compared with those containing crystalloid. This simple observation occurred regardless of the strength of dilution, and on blunt dissection the controls showed better elastic properties. Examination of the remaining serum was negative for fibrinogen and cross-linked fibrin degradation products in both test samples and controls, and there was no difference in full blood count analysis (haemoglobin concentration, red blood cell count and platelet count). Examination of the clots by light microscopy was also similar. There was no difference in clot weights or thrombelastograms between the 0.9% sodium chloride and Ringer's solution controls.

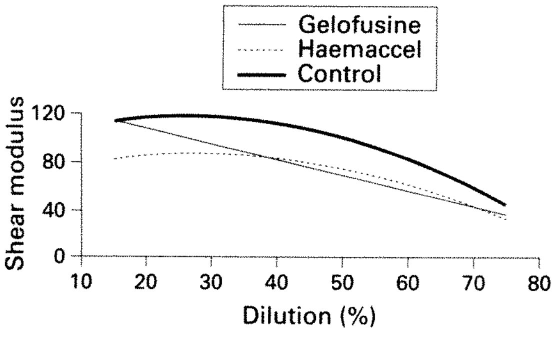

Figure 1 Dose–response curves showing reduction in clot strength (shear modulus) for increasing dilution of fresh blood with the different fluids. Curves were drawn using the best fit from regression analyses (marked † in table 3).

CLOT WEIGHTS

Median clot weights were considerably lower for both plasma substitutes compared with the control solutions (table 1). Median clot weight for Haemaccel was 15.6% lower than that for its control; this value was 25.9% for Gelofusine. These results were significant for Haemaccel and control solutions ($P<0.001$, $z=-3.81$), and Gelofusine and control solutions ($P=0.018$, $z=3.12$).

THROMBELASTOGRAPHY

The elasticity of the plasma substitutes was also considerably lower than that of their controls (table 2). Mean elasticity of the Haemaccel samples was 26.2% lower than that of their controls, and Gelofusine was 22.2% lower. There were significant differences in mean clot strength for both Haemaccel ($P<0.001$, $t=-11.9$) and Gelofusine ($P<0.001$, $t=-7.92$) compared with controls.

The relationship between solutions and dilution levels is plotted in figure 1. The regression models are summarized in table 3. The Haemaccel data showed a quadratic relationship with dilution. By adding the dilution^2 term to the linear model, a significantly greater amount of variation was explained. Gelofusine had a linear relationship with dilution, but in this case the dilution^2 term did not explain enough variation to be added to the equation. The model with the dilution term alone, however, explained 77.1% of the variation observed in the Gelofusine shear modulus. The relationship between saline controls and dilution was similar to that of Haemaccel, but with the higher levels of elasticity observed above.

SCANNING ELECTRON MICROSCOPY

The widespread mesh pattern of fibrin strands seen in the undiluted whole blood control was retained in the 0.9% sodium chloride controls at both dilutions. This reticular network was reduced considerably in

Table 3 Regression models showing possible relationships between clot strength and dilution for individual fluids (mean (SEM)). †Regression analyses producing the best fit

Independent variable	Dependent variable	Beta coefficient	P	Percentage of variance explained
Haemaccel	Dilution	−0.82 (0.13)	<0.001	55.0 (15.9)
Haemaccel	Dilution	1.36 (0.54)	0.02	
	Dilution^2	−0.03 (0.01)	<0.001	69.8 (13.0)†
Gelofusine	Dilution	−1.31 (0.12)	<0.001	77.1 (15.3)†
Gelofusine	Dilution	−1.22 (0.64)	0.07	
	Dilution^2	−0.001 (0.01)	0.88	76.4 (15.5)
Control	Dilution	−1.17 (0.13)	<0.001	55.5 (22.3)
Control	Dilution	1.79 (0.54)	0.002	
	Dilution^2	−0.03 (0.01)	<0.001	69.2 (18.5)†

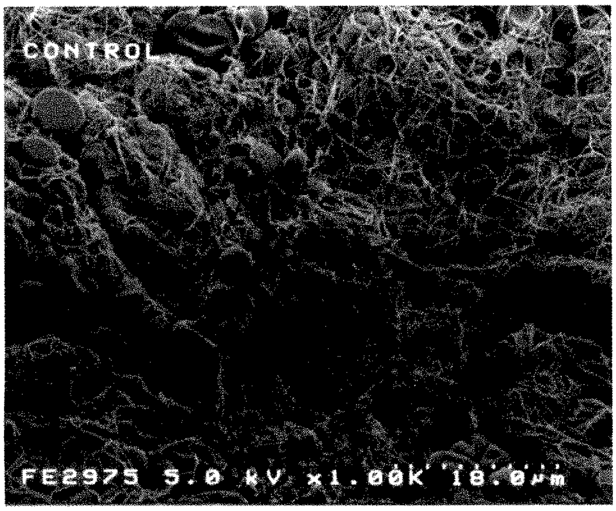

Figure 2 Scanning electron micrograph of whole blood.

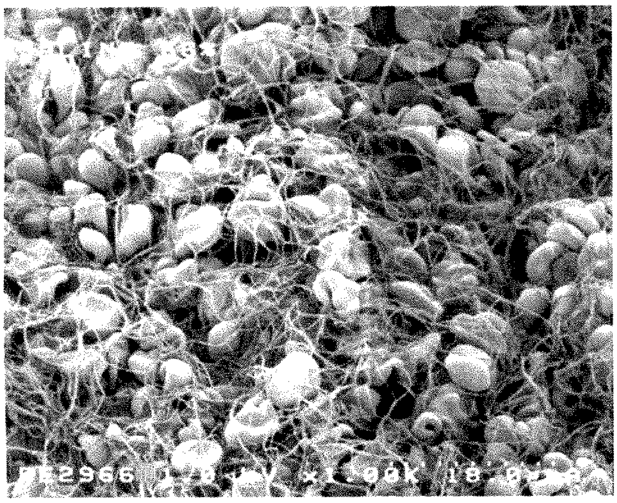

Figure 3 Scanning electron micrograph of whole blood diluted to 66% with 0.9% sodium chloride.

clots containing gelatin-based solutions at 66% dilution (see figs 2–5). The fibrin strands appeared often to be thinner in the test solutions at higher magnification but there was more variation.

Discussion

Gelatin-based plasma substitutes are being used increasingly in the pre-hospital situation and in hospitalized patients requiring massive transfusion. In this situation they may sometimes be the only infusion fluid given together with concentrated red cells, thus producing high concentrations *in vivo.* Some clinicians have an impression that patients resuscitated with gelatin-based colloids develop a tendency to bleed more than those resuscitated with crystalloid, although a search of the literature shows no studies to confirm this. Any increase in bleeding could be a result of either an increase in arterial pressure and perfusion (both of which are clearly easier to achieve with resuscitation using a colloid) or a disturbance in the clotting mechanism. The latter could be because of dilutional and wash-out effects (again reflecting their improved retention in the normal circulation compared with crystalloid) or to interference with the normal coagulation process.

Other colloids used initially in the resuscitation of haemorrhage were found later to interfere with the coagulation process: these include dextran[9] and the hydroxyethyl starches.[10] These effects, principally on factor VIII and platelet adhesion, were detectable using more conventional tests involving measurement of various clotting times. Some workers have reported inhibition of platelet activity by polygeline[11] which is not considered to have a significant effect on coagulation.

One recent study found no significant change in clot strength with Haemaccel but examined only 20% dilution.[12] Another study examining the effects of varying haemodilution on clot strength used proteinaceous solutions and did not include any gelatin-based plasma substitutes.[13] In contrast with our study, they found that these solutions (including albumin) caused a general increase in clot strength compared with saline controls. However, their control dilutions with saline at 25%, 50% and 75% caused a comparable decrease in clot strength to the controls in our study, and furthermore they found similar results when comparing their results *in vitro* with *in vivo* work in rats.

We have shown that *in vitro,* these gelatin-based colloidal solutions reduced the weight of clots while still consuming all of the fibrinogen and trapping similar amounts of red cells and platelets. Therefore, the alteration in clot quality appears to reflect a change in organization of the clot and this is supported by the reduction in elasticity seen macroscopically, when measured with the thrombelastograph and with the arrangement of the fibrin seen on SEM.

Fibronectin is a glycoprotein which forms covalent cross linkages and non-covalent associations with fibrin. These bonds aid the determination of clot architecture and mechanics.[14] Denatured collagen (gelatin) has been shown to bind with fibronectin[15] and polygeline infusion has been shown to decrease plasma fibronectin concentrations *in vivo.*[16] These gelatin-based products may become incorporated into developing clots, thus interfering with polymerization of fibrin monomers and growth of the macromolecular structure of the clot.

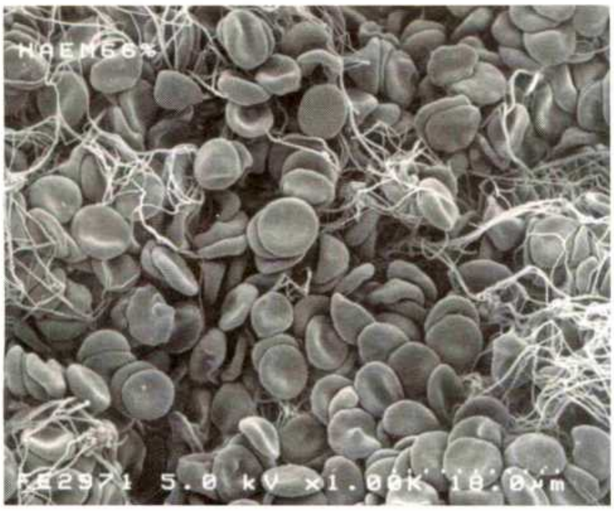

Figure 4 Scanning electron micrograph of whole blood diluted to 66% with polygeline (Haemaccel).

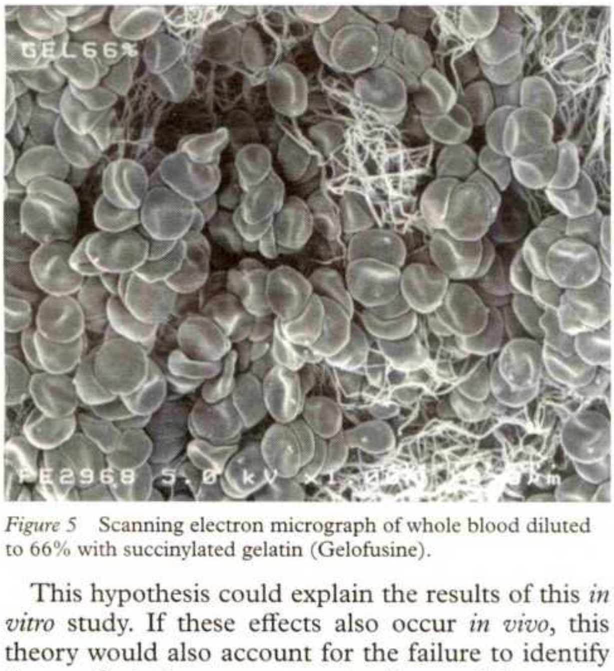

Figure 5 Scanning electron micrograph of whole blood diluted to 66% with succinylated gelatin (Gelofusine).

This hypothesis could explain the results of this *in vitro* study. If these effects also occur *in vivo*, this theory would also account for the failure to identify these effects by measurement of normal haematological variables (such as aPTT and PT tests) which use fibrin formation as an end-point and ignore subsequent events critical to the formation of a viable clot and may not guarantee their safety in situations involving severe or uncontrolled haemorrhage. Any reduction in quality of clot formation would be especially harmful in the pre-hospital situation, where a new clot is being formed, and in patients requiring full haemostatic competence. Studies are needed to explain the mechanism for these observed *in vitro* effects and to determine if they occur *in vivo*.

Acknowledgements

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British Journal of Anaesthesia 1998; **80**: 208–212

Endocrine and metabolic effects of hypotension or halothane inhalation in sheep anaesthetized with pentobarbital

P. M TAYLOR

Summary

We have studied the mechanism whereby halothane induces adrenocortical activity in eight sheep anaesthetized twice for 2 h with pentobarbital. During the second hour they received infusion of nitroprusside to lower mean arterial pressure by 40 mm Hg (group NP) or on another occasion they inhaled 0.5% halothane (group HAL). Plasma concentrations of cortisol, adrenocorticotrophic hormone (ACTH), arginine vasopressin (AVP), glucose and lactate were measured. Infusion of nitroprusside increased cortisol concentrations from mean 44 (SD 33) to 256 (131) nmol litre^{-1} ($P < 0.05$), AVP from 19 (14) to 174 (102) pmol litre^{-1} ($P < 0.05$) and ACTH from 30 (17) to 54 (32) pmol litre^{-1}. Glucose and lactate concentrations did not change significantly. After 60 min of halothane administration, there were fewer effects: plasma cortisol increased from 47 (39) to 63 (44) nmol litre^{-1} ($P > 0.05$) and AVP from 14 (11) to 32 (29) pmol litre^{-1} ($P > 0.05$) while ACTH decreased from 32 (13) to 25 (10) pmol litre^{-1}. The AUC_{60-120} values for all three hormones were significantly lower in group HAL than in group NP ($P < 0.01$). Glucose was unchanged but lactate concentration decreased. These results support, but do not prove, the hypothesis that hypotension is the main stimulus to pituitary–adrenocortical activity during halothane anaesthesia in sheep. A direct effect of nitroprusside cannot be ruled out. (*Br. J. Anaesth.* 1998; **80**: 208–212)

Keywords: anaesthetic techniques, hypotensive; hypnotics barbituate, pentobarbital; anaesthetics volatile, halothane; hormones, adrenal; metabolism, endocrine; sheep

It has long been recognized that noxious stimuli induce an endocrine stress response in mammals, manifested as increased pituitary–adrenocortical (PAC) activity leading to an increase in circulating cortisol.[1] It is also well known that surgery causes a stress response but anaesthesia itself is generally considered to be relatively benign.[2] Taylor[3 4] reported that horses had a marked adrenocortical response to volatile agent anaesthesia which is not seen during i.v. anaesthesia with either propofol, barbiturates, detomidine–ketamine or climazolam–ketamine.[5–8] Sheep have been found to respond to halothane and barbiturate anaesthesia in a manner similar to that of horses[9] and the question arises as to whether or not volatile anaesthesia acts as a noxious stimulus in most species. It is conceivable that in humans, rigorous attention to maintenance of fluid balance and cardiovascular homeostasis during anaesthesia may prevent a stress response from occurring. In addition, as there are few studies in humans where anaesthesia has been investigated in the absence of surgery,[10 11] any effects caused solely by anaesthesia may have been obscured.

It seems likely that some aspect of volatile agent anaesthesia acts as a noxious stimulus inducing a stress response, at least in horses and sheep. It is possible that hypotension and its related effects on perfusion may be responsible. Certainly, haemorrhage is known to cause or enhance adrenocortical activity.[12] However, it is possible that volatile agents may induce an endocrine response by some other unidentified mechanism.

In this study, designed to investigate what stimulates PAC activity during halothane anaesthesia in sheep, an attempt was made to differentiate hypotension from a putative specific effect of halothane. The effects of halothane-free (nitroprusside-induced) hypotension or hypotension-free (sub-anaesthetic doses) halothane exposure were investigated during barbiturate anaesthesia. Pentobarbital was chosen as this does not induce adrenocortical activity.

Materials and methods

ANIMALS

We used eight non-pregnant Welsh Mountain ewes, aged 2–3 yr, weighing 27–39 kg (mean 33 kg) and the study was conducted under Home Office licence PPL 80/83. They were housed indoors with free access to hay and water, except during the 18 h before anaesthesia when they were allowed only water. Each ewe was investigated in two studies, with at least 1 week between anaesthetics. The ewes were prepared for monitoring by surgical exteriorization of the carotid artery into a skin loop at least 2 weeks before the experiment ($n = 2$) or by placement of an indwelling polytetrafluoroethylene catheter in the aorta via the femoral artery at least 3 days before the experiment ($n=6$).[13] Preparatory surgery was performed under halothane anaesthesia. For each experiment, a 14-SWG catheter was inserted in the jugular vein and, when appropriate, a 20-SWG catheter was inserted in the relocated carotid artery approximately 30 min before induction of anaesthesia.

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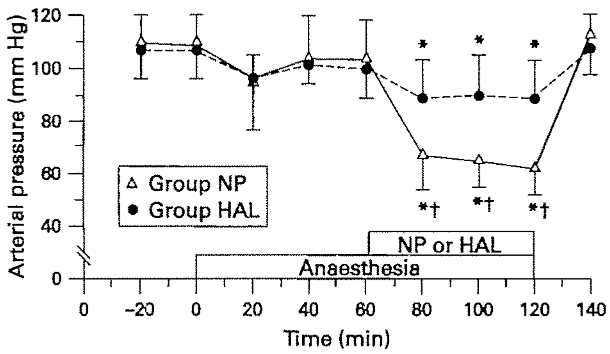

Figure 1 Mean (SD) arterial pressure in eight sheep during pentobarbital anaesthesia. Group NP: nitroprusside-induced hypotension between 60 and 120 min; group HAL: 0.5% inspired halothane between 60 and 120 min. Anaesthesia was induced at 0 min. Pentobarbital infusion was stopped at 120 min. $^*P < 0.05$ compared with control; $^\dagger P < 0.05$ compared with 60-min value. AUC_{60-120} was significantly different between groups ($P < 0.05$).

ANAESTHESIA

Anaesthesia was induced, without premedication, with pentobarbital 16–29 (mean 22) mg kg^{-1} i.v. and the trachea intubated with a cuffed tracheal tube. Anaesthesia was maintained for 2 h with pentobarbital 0.2–0.3 mg kg^{-1} min^{-1} as required, given by incremental doses at 5-min intervals or by infusion (Harvard syringe pump), resulting in a total maintenance dose of 16–39 (mean 31) mg kg^{-1}. The sheep breathed spontaneously throughout anaesthesia and oxygen was supplied either from a circle breathing system or via a T-piece. After 2 h of anaesthesia the sheep were allowed to recover breathing air; the tracheal tube was removed when the swallowing reflex returned.

During the second hour of anaesthesia, sodium nitroprusside was infused to produce hypotension, approximately 40 mm Hg below control values (group NP). A total dose of nitroprusside 405 (162) µg kg^{-1} was given. On another occasion, during the second hour of anaesthesia, the sheep breathed 0.5% (inspired) halothane in oxygen from a T-piece with fresh gas flow rates sufficient to prevent any rebreathing (group HAL). Four of the sheep received nitroprusside first and halothane second. The other four received halothane first and then nitroprusside.

MEASUREMENTS

The femoral or carotid artery catheter was used to record arterial pressure (Lectromed equipment) and for withdrawal of blood samples for pH and arterial blood-gas measurements (Radiometer 130). Heart rate was obtained from the pressure trace and ventilatory frequency by observation of the chest wall. Venous blood samples (5 ml) were obtained for endocrine and metabolite assays. Blood was divided between tubes containing EDTA and heparin and centrifuged immediately at 4 °C; plasma was harvested, frozen and stored at −20 °C until hormone and metabolite assay.

Control measurements were made approximately 20 min after the catheters had been inserted, when the sheep had been standing quietly under minimal restraint in sight of another ewe. A continuous arterial pressure trace was recorded for at least 10 min before any other measurements were made and blood samples obtained. During anaesthesia, sampling took place at 20-min intervals; another sample was obtained 20 min after the end of anaesthesia.

Depth of anaesthesia was monitored by normal clinical assessment, and the same range of pentobarbital infusion rates was used in both groups. The total dose of pentobarbital was 55 (6) mg kg^{-1} in group NP and 53 (4) mg kg^{-1} in group HAL ($P > 0.05$). Time to standing was recorded in minutes from the end of the 2-h anaesthetic period when the animals started to breathe air.

BIOCHEMISTRY

Plasma concentrations of cortisol, adrenocorticotrophic hormone (ACTH) and arginine vasopressin (AVP) were measured using radioimmunoassay (RIA).[14 15] Intra- and inter-assay coefficients of variation were, respectively, for cortisol 5.6% and 11.8%, for ACTH 8.1% and 16.4% and for AVP 16.8% and 21.5%. Plasma glucose and lactate concentrations were measured using standard colorimetric techniques modified for use on an automatic analyser.

STATISTICAL ANALYSIS

Results are given as mean (SD) unless stated otherwise. Changes with time within any study were analysed using analysis of variance (ANOVA) for repeated measures, followed by Dunnett's test to examine deviation from control or 60-min values (as indicated) in each anaesthetic study. Differences between groups were analysed by Student's unpaired *t* test of the area under the time curve taken from control to 20 min after anaesthesia (AUC_{0-140}) and from 60 to 120 min of anaesthesia (AUC_{60-120}).[16] Data that were not normally distributed were subjected to log transformation before analysis. $P < 0.05$ was considered significant.

Results

GROUP NP

Mean arterial pressure (MAP) did not change from control values during the first hour of anaesthesia but during infusion of nitroprusside it decreased significantly ($P < 0.05$) from the 60-min level to mean values of 63–68 mm Hg (fig. 1). MAP returned to control values within 20 min of ceasing nitroprusside and pentobarbital administration. Arterial oxygen tension (Pa_{O_2}) increased ($P < 0.05$) while the sheep inspired a high oxygen fraction; arterial carbon dioxide tension (Pa_{CO_2}) also increased ($P < 0.05$) and pH decreased ($P < 0.05$) (table 1). Heart rate and ventilatory frequency did not change significantly (table 1).

Plasma concentrations of cortisol (fig. 2), ACTH (fig. 3) and AVP (fig. 4) did not change significantly during the first hour of anaesthesia but all increased above the 60 min value thereafter ($P < 0.05$). Glucose and lactate concentrations did not change significantly throughout anaesthesia (table 1).

All sheep in group NP recovered normally and were standing, eating hay within 120 min after the end of anaesthesia.

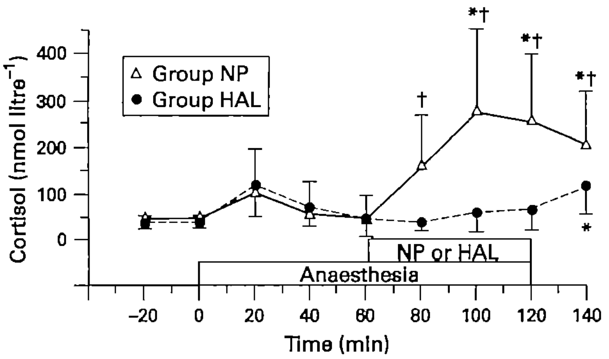

Figure 2 Mean (SD) plasma concentrations of cortisol in eight sheep during pentobarbital anaesthesia. Group NP: nitroprusside-induced hypotension between 60 and 120 min; group HAL: 0.5% inspired halothane between 60 and 120 min. Anaesthesia was induced at 0 min. Pentobarbital infusion was stopped at 120 min. $^*P < 0.05$ compared with control; $^†P < 0.05$ compared with 60-min value. AUC_{60-120} was significantly different between groups ($P < 0.01$).

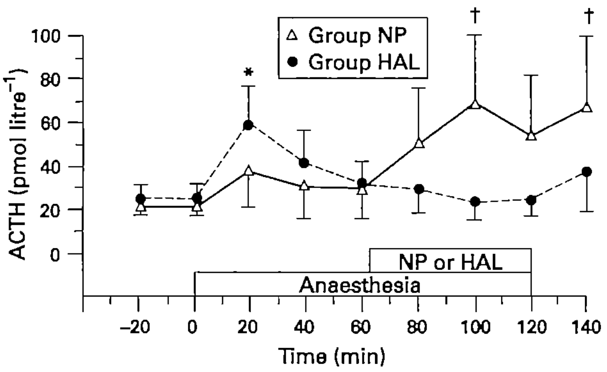

Figure 3 Mean (SD) plasma concentrations of adrenocorticotrophic hormone (ACTH) in eight sheep during pentobarbital anaesthesia. Group NP: nitroprusside-induced hypotension between 60 and 120 min, group HAL: 0.5% inspired halothane between 60 and 120 min. Anaesthesia was induced at 0 min. Pentobarbital infusion was stopped at 120 min. $^*P < 0.05$ compared with control; $^†P < 0.05$ compared with 60-min value. AUC_{60-120} was significantly different between groups ($P < 0.05$).

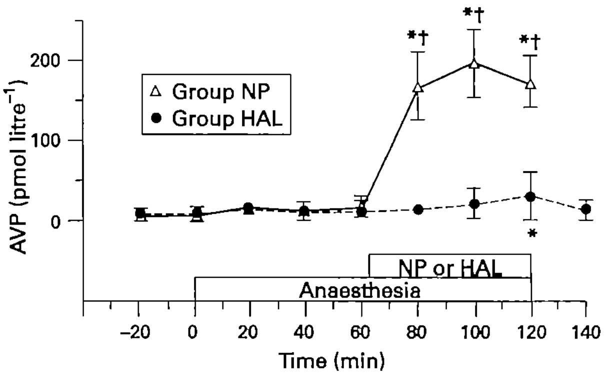

Figure 4 Mean (SD) plasma concentrations of arginine vasopressin (AVP) in eight sheep during pentobarbital anaesthesia. Group NP: nitroprusside-induced hypotension between 60 and 120 min; group HAL: 0.5% inspired halothane between 60 and 120 min. Anaesthesia was induced at 0 min. Pentobarbital infusion was stopped at 120 min. $^*P < 0.05$ compared with control; $^†P < 0.05$ compared with 60-min value. AUC_{60-120} was significantly different between groups ($P < 0.01$).

GROUP HAL

MAP changed little from control values during the first hour of anaesthesia but decreased below control values during halothane administration to mean values of 89–90 mm Hg ($P < 0.05$) (fig. 1). The values recorded during halothane inhalation were not significantly lower than the 60-min value ($P > 0.05$). MAP–AUC_{60-120} was significantly higher than that recorded in group NP ($P < 0.05$). MAP returned to control values within 20 min of ceasing halothane administration. Pa_{O_2} and Pa_{CO_2} increased ($P < 0.05$) during anaesthesia and pH decreased ($P < 0.05$) (table 1). Heart rate did not change significantly (table 1) and ventilatory frequency decreased only transiently at 20 min. There were no significant differences in arterial blood-gas tensions, heart rate or ventilatory frequency between groups HAL and NP.

There were no significant changes in plasma concentrations of cortisol (fig. 2), ACTH (fig. 3) or AVP (fig. 4) during halothane administration and AUC_{60-120} for all three hormones was significantly lower than that recorded in group NP ($P < 0.01$). Glucose concentration did not change but lactate decreased after 60 min, reaching mean values of 0.6 mmol litre^{-1} at 120 min ($P < 0.05$) (table 1). There were no significant differences in glucose or lactate concentrations between groups NP and HAL.

Table 1 Mean (SD) arterial oxygen partial pressure (Pa_{O_2}), arterial carbon dioxide partial pressure (Pa_{CO_2}), pH, heart rate, and plasma glucose and lactate concentrations during pentobarbital anaesthesia in eight sheep with nitroprusside-induced hypotension (group NP) or 0.5% inspired halothane (group HAL). Anaesthesia was induced at 0 min. Pentobarbital infusion was stopped at 120 min Halothane or nitroprusside was given from 60 to 120 min. $^*P<0.05$ compared with control. No significant differences between groups

	Control	20 min	40 min	60 min	80 min	100 min	120 min	140 min
Pa_{O_2} (kPa)								
Group NP	13.9 (2.0)	47.1 (6.8)*	55.2 (6.7)*	58.3 (7.7)*	43.5 (12.9)*	43.3 (10.5)*	47.6 (8.9)*	11.3 (1.3)
Group HAL	12.3 (1.5)	38.8 (14.8)*	45.7 (18.3)*	44.5 (18.7)*	48.5 (18.7)*	48.5 (20.1)*	49.6 (20.1)*	11.7 (1.5)
Pa_{CO_2} (kPa)								
Group NP	4.3 (0.5)	7 2 (0.9)*	7.5 (0.9)*	7.6 (0.9)*	8.0 (0.9)*	7.9 (1.1)*	7 8 (1.1)*	6.8 (1.1)*
Group HAL	4.7 (0.3)	6.9 (1.3)*	7.5 (1 1)*	7.5 (0.9)*	8.1 (0.9)*	8.6 (0.8)*	8.7 (1.2)*	7.2 (0.5)*
pH								
Group NP	7.46 (0.08)	7.30 (0.03)*	7.32 (0.04)*	7.33 (0.04)*	7.33 (0.04)*	7.33 (0.04)*	7.33 (0.04)*	7.39 (0.06)
Group HAL	7.47 (0.03)	7.35 (0.08)*	7.35 (0.06)*	7.34 (0.05)*	7.32 (0.05)*	7.31 (0.06)*	7.30 (0.07)*	7.38 (0.05)*
Heart rate (beat min^{-1})								
Group NP	108 (16)	108 (25)	109 (20)	110 (24)	120 (27)	115 (23)	119 (24)	116 (20)
Group HAL	109 (9)	112 (20)	103 (16)	106 (16)	103 (12)	102 (13)	101 (12)	101 (13)
Glucose (mmol litre^{-1})								
Group NP	3.6 (1.1)	4.2 (0.9)	4.1 (1.0)	4.06 (1.1)	5.3 (1.3)	4.6 (0.4)	4.7 (0.7)	4.9 (1.5)
Group HAL	4.0 (0.5)	4.3 (0.7)	3.9 (0.6)	3.8 (0.7)	3.9 (0.5)	3.7 (0.4)	3.7 (0 3)	3.8 (0.4)
Lactate (mmol litre^{-1})								
Group NP	2.2 (0 5)	2.8 (0.9)	2.3 (0.8)	1.9 (0.6)	2.1 (1.1)	1.9 (0.9)	1.7 (0.2)	2.0 (0.9)
Group HAL	4.0 (1.7)	3.3 (2.2)	2 2 (1.2)	2.4 (2.8)	1.4 (1.0)*	0.7 (0.4)*	0.6 (0.4)*	0.6 (0.3)*

All sheep in group HAL recovered normally; within 120 min after the end of anaesthesia they were standing and eating hay.

Discussion

We have found that nitroprusside-induced hypotension during pentobarbital anaesthesia caused marked PAC activity in sheep; this supports the hypothesis that during halothane anaesthesia, adrenocortical activity is stimulated by hypotension. However, as it proved impossible to give low doses of halothane without causing slight hypotension, it is not clear if the slight PAC stimulation during halothane administration was caused by mild hypotension or by another effect of halothane. It is also impossible to exclude a direct effect of nitroprusside on PAC activity.

Increases in circulating ACTH, AVP and cortisol have been recognized for some time as integral components of the stress response, although the precise changes evoked depend on the nature of the stressor and the species involved.[17] It has long been known that haemorrhage is one such stressor and that it induces PAC activity through stimulation of afferent input from the baroreceptors.[12] Caraty and colleagues[18] demonstrated that haemorrhage in sheep caused an increase in corticotrophin releasing factor (CRF) and AVP concentrations in hypothalamic portal blood (HPB), with a consequent increase in peripheral concentrations of ACTH and cortisol. Unfortunately, they did not report the simultaneous effects on arterial pressure. Nitroprusside-induced hypotension was used by Keller-Wood and Wood[19] as a stressor in a study of PAC behaviour in conscious sheep; results indicated that hypotension alone induced marked PAC activity. The authors reported large increases in plasma ACTH in response to a slightly greater degree of hypotension than that reported in this article. It is conceivable that pentobarbital anaesthesia may blunt the response to hypotension, but the increases in ACTH, AVP and cortisol were substantial none the less. Most investigations into endocrine responses to induced hypotension in humans have been confined to sympathoadrenal activity and the renin–angiotensin–aldosterone axis.[20] [21] Newton and colleagues[22] studied a wider range of endocrine and metabolic responses to induced hypotension during anaesthesia for middle ear surgery and found that three hypotensive methods led only to a minimal endocrine response typical for "low stress" surgery.

AVP is released into the HPB in response to stress and acts as one stimulus to ACTH release.[17] However, it is also involved in cardiovascular homeostasis and is released into the peripheral circulation from the posterior pituitary in response to hypotension and increases in blood osmolarity.[23] AVP is also released in response to atrial firing when filling pressure is reduced.[24] In our study, the relative contribution of hypotension or decreased filling pressure to stimulation of AVP release was not addressed as filling pressures were not measured. The precise role of AVP as a component of the stress response is unclear; its release in response to hypotension can be regarded as a reflex response to maintain cardiovascular stability. However, AVP is also released in response to stimuli such as surgery where arterial pressure is not affected,[25] the amount released appearing to correlate with the degree of surgical stimulus.[26]

The influence of anaesthesia on AVP release is less clear. In a preliminary study, it was shown that some anaesthetics, including halothane, increased circulating AVP, while others such as pentobarbital had little effect. Simpson and Forsling[25] reported that patients anaesthetized with halothane during bypass surgery developed much higher circulating concentrations of AVP than those receiving nitrous oxide only. In contrast, Leighton, Lim and Wilson[27] showed that halothane anaesthesia does not always affect plasma AVP. There is no doubt that AVP is involved in arterial pressure control during anaesthesia, and is increased by hypotension.[28] However, it is likely that the relationship is complex and depends on fluid load and perfusion, not simply on arterial pressure.[29]

Although this study has not been able to confirm that adrenocortical activity induced during halothane anaesthesia is a result of its hypotensive effect, the data are consistent with the hypothesis. If this proves a correct assumption the question arises as to whether or not PAC activity results from hypotension-induced increases in baroreceptor afferent input or from a more fundamental effect associated with hypotension, such as reduced tissue perfusion. Increases in lactate are commonly reported as a component of the metabolic response to surgery[2] but may also relate to reduction in tissue perfusion and an increase in anaerobic metabolism.[30] Lactate decreased during the second hour of anaesthesia in group HAL but did not change in group NP. This suggests that tissue perfusion may have been worse during nitroprusside administration, presumably as a result of hypotension. Inadequate tissue perfusion may act as, or enhance, the stimulus to the stress response during anaesthesia.

In our study, only the inspired halothane concentration was measured as herbivores exhale a substantial amount of methane which affects the output of infrared anaesthetic agent monitors.[31] However, as no rebreathing took place and all sheep experienced similar rates of fresh gas flow, the amount of halothane received was sufficiently similar for the purposes of this study.

No attempt was made to measure cardiac output or any other index of tissue perfusion and there was no evidence that nitroprusside and halothane affected arterial pressure, and thus tissue perfusion, by the same mechanism. Future studies should be directed towards investigating the effect of halothane anaesthesia where normotension is maintained by fluid or inotrope infusion. Inclusion of measures of tissue perfusion would aid interpretation of the data.

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Production of nitrogen dioxide in a delivery system for inhalation of nitric oxide: a new equation for calculation

L. Lindberg and G. Rydgren

Summary

We have evaluated the kinetics of nitrogen dioxide production in a system for inhalation of nitric oxide. In addition to a small fraction of contamination of nitrogen dioxide in the nitric oxide stock gas, a considerable part of the total concentration of nitrogen dioxide is formed immediately after mixing of nitric oxide and oxygen. This initial build-up of nitrogen dioxide is followed by a linear, time-dependent increase in the concentration of nitrogen dioxide. An equation describing the concentration of nitrogen dioxide in the delivery system is formulated: $[NO_2] = k_A \times [NO] + k_B \times [NO]^2 \times [O_2] + k_C \times t \times [NO]^2 \times [O_2]$, where nitrogen dioxide $[NO_2]$ and nitric oxide [NO] concentrations are in parts per million (ppm), oxygen concentration $[O_2]$ is expressed as a percentage and contact time (t) is in seconds. The rate constants are $k_A = 5.12 \times 10^{-3}$, $k_B = 1.41 \times 10^{-6}$ and $k_C = 0.86 \times 10^{-8}$. Calculated nitrogen dioxide values correlated well with measured concentrations. This new finding of an initial build-up of nitrogen dioxide has to be taken into consideration if the conversion of nitric oxide to nitrogen dioxide is to be calculated and in the safety guidelines for the use of nitric oxide. (*Br. J. Anaesth.* 1998; **80**: 213–217)

Keywords: gases non-anaesthetic, nitric oxide; gases non-anaesthetic, nitrogen dioxide; ventilation, mechanical; complications, pulmonary hypertension

Inhaled nitric oxide has emerged as a therapeutic tool in the management of severe respiratory diseases associated with hypoxaemia and pulmonary hypertension.[1] The main problem during inhalation of nitric oxide is its reactivity with oxygen to form the highly toxic nitrogen dioxide.[2] Nitric oxide reacts with water to form nitric and nitrous acids or it may be absorbed by antioxidants in the lungs, producing new free radicals that participate in and delay the occurrence of lung injuries.[3] The oxidation of nitric oxide has been analysed in sealed chambers and has been found to be dependent on nitric oxide and oxygen concentrations, and contact time of nitric oxide with oxygen according to the equation[4 5]:

$$-d[NO]/dt = k \times [NO]^2 \times [O_2] \qquad (1)$$

The rate constant of this equation has been determined for different humidities and temperatures.[6] The equation is used to state safety guidelines for the use of nitric oxide inhalation[7 8] and it has also been claimed that the equation can be used for calculation of nitrogen dioxide concentration in mechanical ventilation systems.[9]

The aim of this study was to analyse the formation of nitrogen dioxide in a delivery system for inhaled nitric oxide and to formulate a mathematical description of nitrogen dioxide production in such a system.

Materials and methods

A Servo Ventilator 300 (Siemens-Elema AB, Solna, Sweden) which delivers oxygen and air via two gas modules with rapid Servo-controlled valves was used. A third similar gas module delivering nitric oxide to the proximal part of the inspiratory limb was attached to the ventilator (fig. 1). Flow in the three gas modules of the ventilator (air, oxygen and nitric oxide) is synchronized to permit constant concentrations of nitric oxide, independent of oxygen concentration, tidal volume and airway pressure.[10]

The gas source was a high-pressure gas cylinder (160 bar) of nitric oxide (999 ± 20 ppm) mixed in nitrogen (AGA AB, Lidingö, Sweden). Contamination of nitrogen dioxide in the cylinder was guaranteed to be less than 20 ppm.

As accurate measurement was of the utmost importance and we wanted to rule out bias from a single technique of measuring nitric oxide and nitrogen dioxide, we chose to analyse these gases both side-stream and main-stream at a fixed distance from the mixing point. Nitric oxide and nitrogen dioxide were analysed side-stream with a chemiluminescence analyser (ML 9841A Monitor Laboratories, LS Lear Siegler; Measurement Controls Corporation, Englewood, CO, USA) and main-stream with electrochemical fuel cells (CiTicels, City Technology Ltd, City Technology Centre, Portsmouth, UK). Calibration of the chemiluminescence analyser and the electrochemical fuel cells was performed with dry calibration gases containing nitric oxide (82.2 ppm ± 2%) and nitrogen dioxide (6.7 ppm ± 2%) in nitrogen (AGA AB, Lidingö, Sweden). The chemiluminescence analyser is zeroed automatically. The electrochemical fuel cells were zeroed to dry air hourly. The system was flushed with fresh nitric oxide–nitrogen four times before the measurements started to eliminate interference from formed and trapped nitrogen dioxide in the high-pressure tubing.

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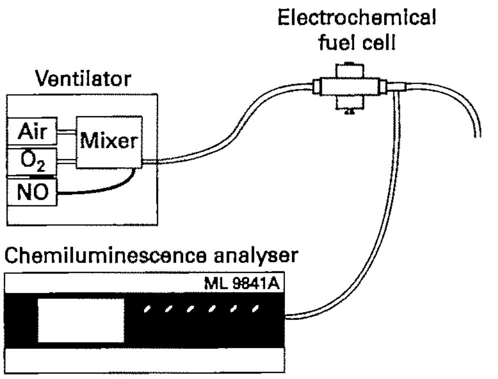

Figure 1 Schematic diagram of the ventilator with paediatric silicon tubes inserted for administering and measuring concentrations of nitric oxide and nitrogen dioxide.

Chemiluminescence analysers use a technique in which nitric oxide reacts with ozone to form excited nitrogen dioxide, which produces a luminescence that is measured spectroscopically. Nitric oxide is measured directly and nitrogen oxides (NO_x) are measured indirectly after passage through a conversion chamber where nitrogen oxides are converted to nitric oxide before measurement. The concentration of nitric oxide produced after the gas has passed this conversion chamber minus the nitric oxide concentration that was directly measured yields the nitrogen dioxide concentration in the sampled gas. Oxygen, carbon dioxide and water vapour can absorb the luminescence, limit the luminescent energy produced and thereby cause underestimation of the actual concentration of nitric oxide and nitrogen dioxide. This process has been referred to as "quenching" and may be more obvious in the measurement of nitrogen dioxide than of nitric oxide.[11] The chemiluminescence analyser was calibrated with nitric oxide–nitrogen dioxide in nitrogen. Measurements were made in gas mixtures of oxygen which introduces quenching and small errors in the measured concentrations of nitric oxide and nitrogen oxides. In order to equate the two measuring techniques, nitric oxide and nitrogen dioxide were measured with the chemiluminescence analyser and electrochemical fuel cells at a standardized point and the measured concentrations were plotted against each other. A linear compensation was made for the difference between the measured concentrations.

Paediatric silicon tubes (diameter 0.009 m) of length 0.9 or 1.47 m were connected to the ventilator. Minute volume ventilation was set at 1, 4, and 7 litre min^{-1} and nitric oxide concentration to 10, 20, 40, 60, 80 and 100 ppm at four different FI_{O_2} values (0.21, 0.4, 0.7 and 0.9). To avoid contamination with room air, we added a 0.6-m tube after the monitors, and the system was open to atmospheric air to avoid pressure dependency (fig. 1).

Contact time of nitric oxide with oxygen was calculated by dividing the volume of the tube system with mean gas flow. Nitrogen dioxide concentrations were plotted against contact time of nitric oxide and oxygen in the inspiratory tube at nitric oxide 10, 50, and 100 ppm and an FI_{O_2} of 0.9.

The oxidation of nitric oxide to nitrogen dioxide and the ultimate nitrogen dioxide concentration in the delivery system was analysed and described by the following formula:

$$[NO_2] = k_A \times [NO] + k_B \times [NO]^2 \times [O_2] + k_C \times t \times [NO]^2 \times [O_2] \qquad (2)$$

where nitrogen dioxide $[NO_2]$ and nitric oxide [NO] concentrations are in parts per million (ppm), oxygen concentration $[O_2]$ is expressed as a percentages and contact time (t) is in seconds. k_A, k_B and k_C are rate constants. The rate constants were determined from 210 different combinations of nitric oxide and oxygen concentrations and contact times by curve fitting analysis. A linear regression analysis was performed between calculated concentrations of nitrogen dioxide and measured values.

The rate constant in equation (1) was also determined from nitric oxide and oxygen concentrations and contact times by curve fitting analysis. A linear regression analysis was performed between calculated and measured concentrations of nitrogen dioxide. The concentration of oxygen was converted to ppm and time to minutes to agree with previously published rate constants.[9]

STATISTICAL ANALYSIS

Curve fitting analysis and linear regression were performed in Statistica 5.0 for Windows (StatSoft, Inc. Tulsa, OK, USA). Difference between methods was assessed by calculating bias (mean difference between two values) and precision (SD of the mean differences) based on the method proposed by Bland and Altman.[12]

Results

The concentration of nitric oxide measured by the chemiluminescence analyser was underestimated by 3.5% and the concentration of nitrogen oxides (NO_x) by 3.4% compared with the electrochemical fuel cells. The measured concentrations of nitric oxide and nitrogen oxides were linearly corrected to compensate for these underestimations. After this correction for oxygen-dependent quenching in the chemiluminescence analyser, concentrations of nitric oxide and nitrogen dioxide measured by the

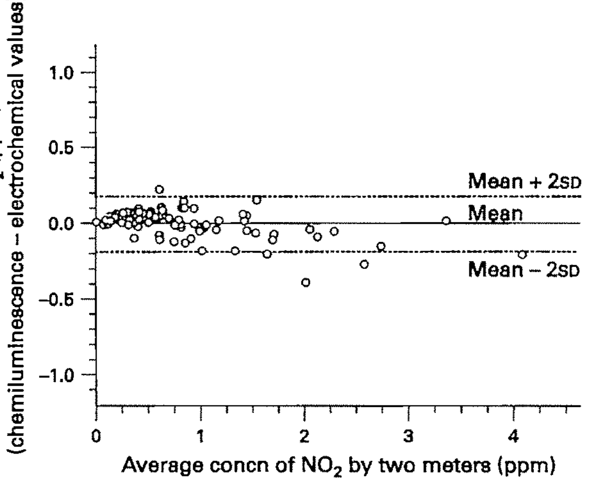

Figure 2 Difference in nitrogen dioxide (NO_2) concentrations measured by the chemiluminescence analyser after correction for quenching and the electrochemical fuel cell, plotted against the mean of the two methods. The limits of agreement (± 0.18 ppm (± 2SD)) are small enough to show that the measurements have good accuracy.

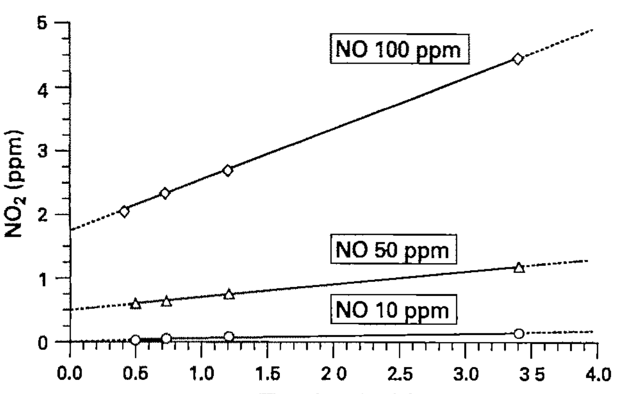

Figure 3 Nitrogen dioxide (NO_2) concentrations measured by the electrochemical fuel cell at different contact times between nitric oxide and oxygen, at nitric oxide concentrations of 10, 50 and 100 ppm and an Fi_{O_2} of 0.9. Note the intercept at time zero.

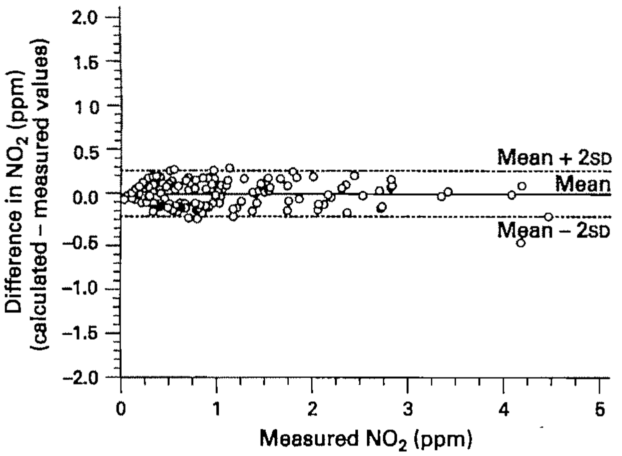

Figure 4 Difference between values of nitrogen dioxide (NO_2) calculated by equation (2) $[NO_2] = k_A \times [NO] + k_B \times [NO]^2 \times [O_2] + k_C \times t \times [NO]^2 \times [O_2]$ and measured, plotted against measured concentrations of NO_2. The limits of agreement (0.29 and −0.22 ppm) are small enough to conclude that the agreement between calculated and measured values is good.

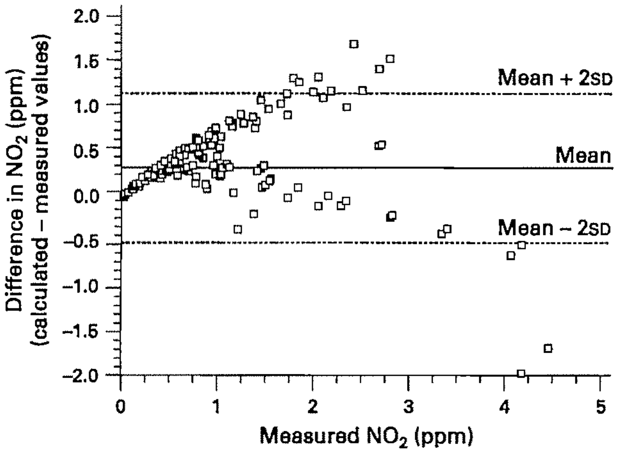

Figure 5 Difference between values of nitrogen dioxide (NO_2) calculated by equation (1) $-d[NO]/dt = k \times [NO]^2 \times [O_2]$ and measured, plotted against measured concentrations of NO_2. The limits of agreement (1.14 and −0.50 ppm) and the plotted values illustrate the lack of agreement between calculated and measured values.

electrochemical fuel cell and the chemiluminescence analyser agreed well. Difference in nitrogen dioxide concentration measured by the chemiluminescence analyser after correction, and the electrochemical fuel cell, was within ± 0.18 ppm (±2 SD) (fig. 2).

The concentration of nitrogen dioxide increased linearly during the contact time of 0.5–3.5 s. At an Fi_{O_2} of 0.9, nitrogen dioxide was produced at an approximate rate of 0.045, 0.21 and 0.8 ppm s^{-1} with nitric oxide 10, 50 and 100 ppm, respectively (fig. 3). Calculated initial concentrations of nitrogen dioxide found by extrapolation of measured concentrations of nitrogen dioxide in figure 3 to contact time zero were 0.031, 0.51 and 1.75 ppm with nitric oxide 10, 50 and 100 ppm, respectively.

The rate constants in equation (2) at 21°C dry gases were: $k_A = 5.12 \times 10^{-3}$, $k_B = 1.41 \times 10^{-6}$ and $k_C = 0.86 \times 10^{-6}$.

Calculated nitrogen dioxide concentrations using equation (2) correlated well with measured nitrogen dioxide concentrations in the system ($r^2 = 0.98$) and showed good agreement when the difference between calculated and measured values was plotted against measured concentration of nitrogen dioxide. The limits of agreement were 0.29 and −0.22 ppm (fig. 4).

The rate constant in equation (1) at 21°C dry gases was 1.89×10^{-6} ppm^{-1} $\%^{-1}$ s^{-1} (11.3×10^{-9} ppm^{-2} min^{-1}). Calculated nitrogen dioxide concentrations using equation (1) correlated less than equation (2) with measured concentrations ($r^2 = 0.82$). A plot of the difference between calculated and measured values against measured concentrations of nitrogen dioxide illustrates the lack of agreement. The limits of agreement were 1.14 and −0.50 ppm (fig. 5).

Nitrogen dioxide concentrations at the Y-piece, with a 0.9-m long paediatric tube and a flow of 2 litre min^{-1} at different mixtures of nitric oxide and oxygen, were calculated according to equation (2) describing nitrogen dioxide production in the delivery system (table 1). Nitrogen dioxide concentrations of 1 and 2 ppm are indicated in order to highlight the concentrations of nitric oxide and oxygen at which these levels were reached.

Discussion

We have found that the previously published equation (1)[5] describing the oxidation of nitric oxide in a closed system with constant concentrations of nitric oxide and oxygen is unsuitable for describing the conversion of nitric oxide to nitrogen dioxide in our delivery system for inhalation of nitric oxide. Our measurements indicate that the oxidation of nitric oxide takes place in two steps, a rapid build-up reaction followed by a linear, time-dependent reaction. A new equation describing the oxidation of nitric oxide to nitrogen dioxide was formulated as a result of the following.

A small contamination of nitrogen dioxide from the nitric oxide stock gas tank contributed to the nitrogen dioxide concentration. As contamination of nitrogen dioxide is dependent on the stock gas concentration of nitric oxide, it was assumed to be proportional to the stock gas concentration of nitric oxide:

$$k_A \times [NO] \quad (2a)$$

An initial build-up of nitrogen dioxide became apparent when the linear, time-dependent increase in nitrogen dioxide concentration was extrapolated to the Y axis (fig. 3). The influence of nitric oxide and oxygen concentrations on this initial build-up of

Table 1 Calculation of nitrogen dioxide concentrations in the delivery system at different nitric oxide and oxygen concentrations, at an inspiratory flow of 2 litre min^{-1} (neonatal) and with a paediatric tube (diameter 0.009 m) with a length of 0.9 m. Nitrogen dioxide concentrations of 1 and 2 ppm are indicated in bold type and bold and underlined type, respectively

	Oxygen concentration (%)						
NO (ppm)	21	35	50	60	70	80	90
10	0.06	0.06	0.06	0.07	0.07	0.07	0.08
20	0.12	0.14	0.16	0.17	0.18	0.20	0.21
30	0.20	0.24	0.28	0.31	0.34	0.37	0.39
40	0.30	0.37	0.44	0.49	0.54	0.59	0.64
50	0.40	0.51	0.63	0.70	0.78	0.86	0.93
60	0.52	0.68	0.84	0.95	**1.06**	**1.17**	**1.28**
70	0.66	0.87	**1.09**	**1.24**	**1.39**	**1.54**	**1.69**
80	0.80	**1.07**	**1.37**	**1.56**	**1.76**	**1.96**	**2.15**
90	0.96	**1.31**	**1.68**	**1.92**	**2.17**	**2.42**	**2.67**
100	**1.13**	**1.56**	**2.02**	**2.32**	**2.63**	**2.93**	**3.24**

nitrogen dioxide, which appears at a contact time of 0–0.5 s, was analysed. Different exponential coefficients for the concentrations of nitric oxide and oxygen were tested in a non-linear multiple regression analysis. The build-up of nitrogen dioxide was found to be directly proportional to the concentration of oxygen and to the square of the nitric oxide concentration, and under this condition was independent of time:

$$k_B \times [NO]^2 \times [O_2] \tag{2b}$$

The linear and time-dependent increase in the concentration of nitrogen dioxide is in agreement with the previously published equation describing the oxidation of nitric oxide with oxygen:

$$k_C \times t \times [NO]^2 \times [O_2] \tag{2c}$$

Theoretically the equation is:

$$k_C \times (1-e^{-t/\tau}) \times [NO]^2 \times [O_2] \tag{2d}$$

where τ = time constant and the factor $(1-e^{-t/\tau})$ shows that as time advances, the rate of change decreases towards zero and the final nitrogen dioxide concentration approaches a final limiting value. The graph of equation (2d) is therefore non-linear. In this case the non-linear behaviour corresponds to the consumption and limited amount of nitric oxide in the gas mix. When all nitric oxide is consumed no more nitrogen dioxide can be formed. For short contact times and small values of nitrogen dioxide, such as appear in a delivery system, the graph appears linear.

The initial production of nitrogen dioxide has not been described in earlier kinetic studies on the reaction between nitric oxide and oxygen.[13] However, it has been noticed that there is an almost instantaneous increase in nitrogen dioxide concentration during air pollution with nitric oxide.[14] One possible reason why this early formation of nitrogen dioxide has not been observed is that kinetic analysis has been carried out in a closed system with a constant concentration of nitric oxide and oxygen in order to avoid the instability that appears during the mixing procedure of the gases. Another reason is that very fast nitrogen dioxide analysers are not available. We were able to estimate the immediate build-up phase by extrapolation.

It seems plausible that the initial production of nitrogen dioxide occurs at the mixing point as a result of a high mixing stock gas concentration of nitric oxide in a fairly high and constant concentration of oxygen. However, it has been noticed that nitrogen dioxide immediately re-forms after a soda lime absorber[15] and that some surfaces have catalytic activity and can increase the rate of nitric oxide oxidation.[14] We used silicon tubes that are claimed not to affect nitric oxide or nitrogen dioxide concentrations.[15] This implies that the mixing concentrations of nitric oxide and oxygen may affect nitrogen dioxide production, but that a rapidly achieved equilibrium in the reaction between nitric oxide and oxygen may explain the initial increase in concentration of nitrogen dioxide.

The agreement between measured and calculated concentrations of nitrogen dioxide also indicates the accuracy of equation (2) and our findings. Equation (2) makes it possible to calculate accurately the concentration of nitrogen dioxide at different set concentrations of nitric oxide and oxygen at different contact times. Documentation of the expected concentration of nitrogen dioxide is of value when set nitric oxide and oxygen concentrations are decided. In table 1 we have calculated nitrogen dioxide concentrations at different set concentrations of nitric oxide and oxygen with settings appropriate to paediatric ventilation, where a high concentration of nitrogen dioxide can be expected. The delivered nitrogen dioxide concentration in the system was always less than 1 ppm if nitric oxide was less than 50 ppm, independent of oxygen concentration, but additional formation takes place in the airway of the patient also, and therefore the alveolar concentration must be expected to be higher.

Equation (1) has been used to calculate and recommend safety guidelines for the use of nitric oxide inhalation. We determined the rate constant of equation (1) and found expectedly that the equation did not accurately describe the concentration of nitrogen dioxide in the delivery system. The rate constant in equation (1) in the current study is higher than has been published previously,[5-8] but similar to the rate constant which Nishimura and co-workers found when nitric oxide was blended with air before introduction into a ventilator.[9] The differences between the rate constants could be because we used a dynamic system where the final concentration of nitrogen dioxide was used for calculation.

Because of the unexpected and previously undescribed finding of a very early high concentration of nitrogen dioxide it was important that accurate measurements were performed. In order to rule out bias from one single technique of measurement we chose to use a chemiluminescence analyser and electrochemical fuel cells. However, both techniques have problems and to equate them we had to compare and analyse measured concentrations.

Electrochemical fuel cells and chemiluminescence analysers are at present the methods of choice to measure nitric oxide and nitrogen dioxide. The chemiluminescence analyser is usually preferred as it offers a more accurate reading of nitric oxide, especially during prolonged measurements. The chemiluminescence technique was designed for environmental monitoring and was not intended to be used in high oxygen environments, but it is also used by gas manufacturers to measure nitric oxide concentration. The effect of quenching was the main reason for the underestimation of measured concentrations of nitric oxide and nitrogen dioxide by the chemiluminescence analyser, but after correction there was good agreement between the chemiluminescence analyser and the electrochemical fuel cells.

Safety guidelines for the use of nitric oxide have referred to kinetic gas reaction analysis in closed systems of constant concentrations of nitric oxide and oxygen, and have therefore exclusively noted the time-dependent oxidation of nitric oxide. An initial build-up of nitrogen dioxide, which seems to appear immediately after mixing of nitric oxide and oxygen, has to be taken into consideration and will result in higher concentrations of nitrogen dioxide than have been assumed previously.

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Lidocaine increases the ventricular fibrillation threshold during bupivacaine-induced cardiotoxicity in pigs

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Summary

Ventricular fibrillation (VF) is a cause of death in bupivacaine-induced cardiovascular toxicity. We have examined the therapeutic effects of lidocaine on the threshold for bupivacaine-induced VF in *in situ* beating swine hearts. Twenty-four animals were allocated to one of three groups: 0.25% bupivacaine, 1% lidocaine or 0.25% bupivacaine with 1% lidocaine were infused into the left anterior descending coronary artery in increasing doses of 0, 1, 2, 4, 8 and 16 ml h^{-1} for 15 min, respectively. ECG and haemodynamic variables were monitored continuously during infusion. Regional myocardial function in the area supplied by the left anterior descending coronary artery was assessed using the sonomicrometry technique. VF did not occur in the lidocaine group. VF developed at higher infusion rates in animals given bupivacaine with lidocaine (in one animal at an infusion rate of 8 ml h^{-1} and in seven at 16 ml h^{-1}) compared with animals given bupivacaine alone (in one at an infusion rate of 4 and in seven at 8 ml h^{-1}). Although regional myocardial function decreased with increases in the infusion rate in each group, the depressant effects of the bupivacaine solution (medial inhibitory infusion rate of systolic shortening: IR_{50} = 2.43 (0.43) ml h^{-1}) were significantly greater than those of the lidocaine solution (IR_{50} = 5.83 (0.87) ml h^{-1}), but did not differ from those of the bupivacaine with lidocaine solution (IR_{50} = 3.54 (0.56) ml h^{-1}). This study indicates that a combination of lidocaine and bupivacaine increased the threshold for bupivacaine-induced VF without further depressing myocardial contractility. (*Br. J. Anaesth.* 1998; **80**: 218–222)

Keywords: anaesthetics local, bupivacaine; anaesthetics local, lidocaine; heart, arrhythmia, fibrillation; complications, arrhythmia

Bupivacaine-induced cardiotoxicity is characterized by depression of myocardial conductance and contraction. While recent reports,[1-3] including one from our laboratory, have demonstrated that amrinone reverses depressed myocardial contractility, there is no accepted therapy to correct conduction abnormality. Correction or avoidance of conduction abnormality is important because tachyarrhythmias and ventricular fibrillation (VF) caused by bupivacaine-induced cardiotoxicity may be fatal.[4] The mechanism of myocardial conduction abnormality has been explained by the receptor modulated theory.[5] Bupivacaine leads to enhanced myocardial sodium channel block during a cardiac cycle because it dissociates slowly during diastole (fast in, slow out), unlike lidocaine which dissociates from the myocardial sodium channels swiftly during diastole (fast in, fast out). The modulated receptor hypothesis has been extended for a mixture of local anaesthetics which compete for the same binding site of the sodium channel.[6] In an *in vitro* study using guinea pig ventricular myocardium, it has been shown that a drug with rapid binding and unbinding kinetics, such as lidocaine, displaces a drug with slower binding kinetics, such as bupivacaine, resulting in less sodium channel block with the combination of the two drugs than that produced by bupivacaine alone. However, the beneficial effects of lidocaine on bupivacaine-induced cardiotoxicity have not been demonstrated *in vivo*.

We hypothesized that, if the theory is true, *in vivo* the combination of lidocaine and bupivacaine should result in a higher VF threshold than that with bupivacaine alone. As there is a possibility that myocardial contractility might be depressed further by such a combination than by bupivacaine alone,[7] this combination should be examined before clinical use of lidocaine in bupivacaine-induced cardiotoxicity. Therefore, we examined the hypothesis and the effects on myocardial contractility *in vivo* using an animal model similar to that used in our laboratory.[3 8]

Materials and methods

The study was approved by the Animal Research Committee of Kawasaki Medical School (No. 95–048). Twenty-four pigs, weighing 25–43 kg, were anaesthetized with pentobarbital 600 mg i.v. after administration of ketamine 500 mg i.m. The trachea was intubated and the lungs ventilated with a tidal volume adjusted to maintain normocapnia (4.7–5.3 kPa) and a ventilatory frequency of 15 bpm. Anaesthesia was maintained with 50% nitrous oxide and 2–3% sevoflurane during surgical preparation. After instrumentation, sevoflurane was discontinued, and fentanyl was infused at a rate of 0.5 mg h^{-1} to the end of the experiment. Neuromuscular block was maintained with pancuronium 4 mg h^{-1} throughout

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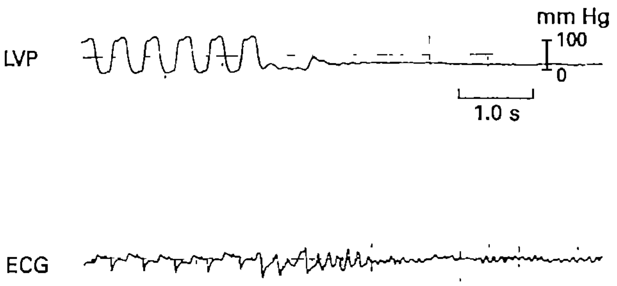

Figure 1 Ventricular fibrillation induced by intracoronary infusion of 0.25% bupivacaine 8 ml h^{-1}. Left ventricular pressure (LVP) and ECG tracing at 25 mm cm^{-1} are shown. Note the widened QRS complex and ST depression R-on-T type PVC preceded ventricular fibrillation.

the study. Rectal temperature was maintained at approximately 37–38 °C by a water blanket.

SURGICAL PREPARATION

The right carotid artery and right external jugular vein were cannulated. Ringer's lactate solution was infused at a rate of 10 ml kg^{-1} h^{-1} during surgical preparation and at a rate of 5 ml kg^{-1} h^{-1} via a venous catheter after surgical preparation. After median sternotomy, a 14-mm ultrasonic transit-time flow probe was placed around the root of the ascending aorta for measurement of cardiac output (CO) via a flowmeter (T208; Transonic Systems Inc., New York, NY, USA). Animals were then turned from the supine to the right lateral position. Left thoracotomy and pericardiotomy were performed through the fifth intercostal space, and the heart was placed in a pericardial cradle. The left anterior descending coronary artery (LAD) was dissected free, proximal to the first diagonal branch, to measure its blood flow (Q_{LAD}) using an ultrasonic flow probe (2 mm in diameter). The value was corrected for myocardial weight. Then a 22-gauge catheter was inserted into the LAD via a puncture and advanced 0.5–1.0 cm in the retrograde direction for infusion of local anaesthetics. Another catheter was placed in the anterior interventricular vein for blood sampling. A pre-calibrated micromanometer catheter (7.5 Fr. Goodtec, Huntington Beach, CA, USA) was inserted into the left ventricle to measure left ventricular pressure through the apex of the heart. Regional myocardial function was evaluated by the sonomicrometry technique, as described previously.[8] A pair of ultrasonic dimension crystals were placed in an equatorial plane into the subendocardium supplied by the LAD for measurement of segmental length. The signals of ventricular pressure and sonomicrometry were digitized at 250 Hz via a computer interface with a 12-bit analogue-to-digital converter and stored for subsequent analysis. The percent systolic segment shortening (SS) was calculated off-line from the following formula: SS = (EDL − ESL) × EDL^{-1} × 100, where EDL= end-diastolic segment length and ESL= end-systolic segment length during a cardiac cycle. SS was normalized to the baseline values of each animal.

STUDY DESIGN

Animals were allocated randomly to one of the following three groups: bupivacaine (Bup: n = 8, mean 27.0 (SEM 0.4) kg), lidocaine (Lid: n = 8, 32.4 (1.4) kg) or bupivacaine with lidocaine (Bup + Lid: n = 8, 33.4 (1.1) kg). One of three saline solutions containing 1% lidocaine, 0.25% bupivacaine or 1% lidocaine with 0.25% bupivacaine, respectively, was infused at increasing rates of 0, 1, 2, 4, 8 and 16 ml h^{-1} for 15 min into the LAD with a syringe pump (STC-521, Terumo, Tokyo, Japan) via the catheter in animals of the corresponding groups. When VF occurred, resuscitation was not attempted and the experiment was terminated. Haemodynamic measurements and blood sampling were carried out after at least 10 min of each infusion rate. Blood samples obtained from the interventricular vein were used for measurement of plasma concentrations of lidocaine and bupivacaine using a fluorescence polarization immunoassay and high-pressure liquid chromatography, respectively.

Table 1 Occurrence of ventricular fibrillation and death during intracoronary infusion of local anaesthetics. There was a significant difference between the bupivacaine (Bup) compared with the bupivacaine and lidocaine (Bup+Lid) group (Mann–Whitney *U* test, $P<0.05$)

Group	Infusion rate (ml h^{-1}) 1	2	4	8	16
Bup (n=8)	0	0	1	7	—
Lid (n=8)	0	0	0	0	0
Bup+Lid (n=8)	0	0	0	1	7

DATA ANALYSIS

Data are expressed as mean (SEM). Statistical analysis of data during baseline (0 ml h^{-1} infusion rate) and during infusion of local anaesthetics into the LAD was performed by one-way analysis of variance (ANOVA) followed by Fisher's least significant difference test. Pairwise comparisons on the corresponding steps were performed by Student's *t* test with Bonferroni's correction. The inhibitory infusion rates of local anaesthetics for 50% SS (IR_{50}) were calculated from dose–response curves of normalized SS *vs* infusion rate. The Mann–Whitney *U* test was used to compare the distribution of VF at different infusion rates. $P < 0.05$ was considered statistically significant.

Table 2 Plasma concentrations (mean (SEM)) of local anaesthetics in anterior intraventricular vein blood. Number of samples was 8 except for ^{a}(n=6) and ^{b}(n=2). The reductions in sample numbers were the result of death caused by VF before blood sampling from the anterior intraventricular vein

Group	Infusion rate (ml h^{-1}) 1	2	4	8	16
Group Bup					
Bupivacaine	1.4 (0.5)	2.0 (0.3)	4.0 (0.4)	7.6 (0.9)^{a}	—
Group Lid					
Lidocaine	1.5 (0.2)	4.8 (0.7)	11.1 (1.1)	29.5 (2.6)	58.3 (6.7)
Group Bup+Lid					
Lidocaine	2.5 (0.5)	5.3 (1.0)	12.8 (3.0)	29.0 (7.1)	33.7 (8.9)^{b}
Bupivacaine	1.3 (0.4)	2.0 (0.3)	3.3 (0.3)	6.6 (0.5)	12.6 (0.6)^{b}

Table 3 Changes in electrocardiographic intervals (mean (SEM)). *$P<0.05$ compared with baseline; †$P<0.05$ compared with group Lid

	Infusion rate (ml h^{-1})					
	0 (baseline)	1	2	4	8	16
PQ (cs)						
Group Bup	9.2 (0.4)	9.3 (0.4)	9.2 (0.3)	9.6 (0.3)	9.3 (0.3)	—
Group Lid	9.2 (0.5)	9.4 (0.4)	9.4 (0.4)	9.4 (0.4)	9.3 (0.5)	9.2 (0.4)
Group Bup+Lid	9.3 (0.5)	9.2 (0.5)	9.3 (0.4)	9.6 (0.4)	9.3 (0.5)	9.6 (0.5)
QRS (cs)						
Group Bup	5.9 (0.5)	6.0 (0.5)	6.1 (0.4)	7.4 (0.9)*†	9.3 (0.7)*†	—
Group Lid	6.2 (0.5)	6.1 (0.4)	6.1 (0.4)	5.8 (0.4)	6.1 (0.4)	6.2 (0.4)
Group Bup+Lid	5.9 (0.7)	5.9 (0.5)	6.0 (0.6)	6.1 (0.6)	8.7 (1.0)*	11.0 (0.5)*†
QTc (cs)						
Group Bup	27.0 (1.1)	28.4 (1.6)	27.8 (1.3)	27.1 (1.6)	28.8 (1.8)	—
Group Lid	28.3 (2.1)	27.0 (1.4)	26.6 (1.0)	25.4 (1.3)	25.9 (1.1)	26.5 (0.7)
Group Bup+Lid	27.1 (0.7)	27.2 (1.0)	26.8 (1.2)	26.3 (1.3)	25.3 (1.8)	26.1 (1.7)

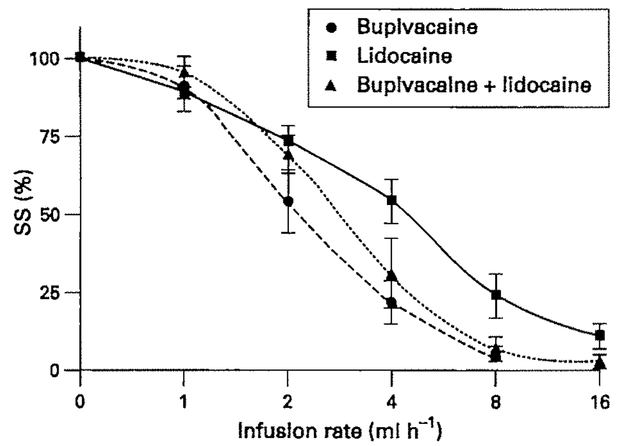

Figure 2 Normalized systolic segment shortening (SS) of the LAD region during intracoronary infusion of local anaesthetics (1% lidocaine, 0.25% bupivacaine or 1% lidocaine with 0.25% bupivacaine). SS decreased in a dose-dependent manner in the three groups. The infusion rate for 50% inhibition of SS (IR$_{50}$) was significantly greater during infusion of lidocaine (5.83 (0.87) ml h^{-1}) than during infusion of bupivacaine or bupivacaine with lidocaine (2.43 (0.43), 3.54 (0.56) ml h^{-1}, respectively).

Results

Mean body weight in group Bup was significantly less than those of the other groups. ECG and LVP tracings made when VF occurred during bupivacaine infusion are shown figure 1. VF was triggered by an R-on-T type ventricular premature beat in all animals without any preceding arrhythmias, except in one animal in group Bup, in which bigeminy developed. No VF occurred in group Lid at any infusion rate (table 1). VF developed in one animal at an infusion rate of 4 ml h^{-1} and in seven at a rate of 8 ml h^{-1} in group Bup, and in one animal at a rate of 8 ml h^{-1} and in seven at a rate of 16 ml h^{-1} in group Bup+Lid. There was a significant difference between groups Bup and Bup+Lid. Table 2 summarizes the mean plasma concentrations in anterior intraventricular vein blood during stepwise increases in intracoronary infusion rates of local anaesthetics. Based on the data in tables 1 and 2, no VF was observed in groups Bup and Bup+Lid at plasma vein concentrations of bupivacaine of less than 2.0 (0.3) and 3.3 (0.3) μg ml^{-1}, respectively. A lidocaine concentration of less than 58.3 (6.7) μg ml^{-1} was not associated with VF.

Substantial ECG changes occurred at higher infusion rates of local anaesthetics (table 3). Widening of the QRS complex with increasing infusion rate was observed at infusion rates of 4 and 8 ml h^{-1} in group Bup, and at 8 and 16 ml h^{-1} in group Bup+Lid, but not in group Lid. PQ and QTc intervals did not change significantly. ST-T wave depression was common with intracoronary infusion of higher doses of local anaesthetics.

Haemodynamic data during intracoronary infusion of local anaesthetics are presented in table 4. There were no significant differences in haemodynamic variables such as HR, MAP, CO and Q_{LAD} between the three groups. Although these variables did not change from baseline during stepwise

Table 4 Haemodynamic variables (mean (SEM)) during intracoronary infusion of lidocaine (Lid), bupivacaine (Bup), and lidocaine with bupivacaine (Bup+Lid). HR=Heart rate, MAP=mean arterial pressure, CO=cardiac output, Q_{LAD}=left anterior coronary blood flow. *$P<0.05$ compared with baseline. n=8 except for ^{a}n=7

	Infusion rate (ml h^{-1})					
	0 (baseline)	1	2	4	8	16
HR (beat min^{-1})						
Group Bup	117 (4)	116 (5)	119 (5)	122 (5)	123 (5)^{a}	—
Group Lid	107 (6)	104 (5)	111 (5)	111 (4)	114 (4)	115 (5)
Group Bup+Lid	101 (6)	115 (6)	113 (6)	115 (5)	114 (5)	124 (6)*
MAP (mm Hg)						
Group Bup	92 (3)	89 (2)	86 (2)	87 (2)	84 (3)*^{a}	—
Group Lid	94 (4)	90 (3)	89 (3)	85 (3)	85 (2)	85 (9)
Group Bup+Lid	93 (2)	97 (2)	84 (2)	85 (2)	79 (3)*	76 (2)*^{a}
CO (litre min^{-1})						
Group Bup	2.0 (0.2)	2.0 (0.2)	1.9 (0.1)	1.9 (0.2)	1.9 (0.1)^{a}	—
Group Lid	2.0 (0.2)	2.0 (0.1)	2.0 (0.2)	1.9 (0.2)	1.9 (0.1)	2.0 (0.2)
Group Bup+Lid	2.2 (0.1)	2.1 (0.1)	2.1 (0.1)	2.0 (0.1)	1.9 (0.1)*	1.8 (0.1)*^{a}
Q_{LAD} (ml min^{-1} g^{-1})						
Group Bup	0.92 (0.07)	0.82 (0.11)	0.77 (0.10)	0.74 (0.09)*	0.71 (0.13)^{a}	—
Group Lid	0.94 (0.05)	0.88 (0.07)	0.78 (0.06)	0.74 (0.06)	0.69 (0.05)	0.76 (0.05)
Group Bup+Lid	1.02 (0.12)	1.00 (0.09)	0.84 (0.08)	0.72 (0.07)*	0.62 (0.06)*	0.57 (0.05)*^{a}

increases in lidocaine infusion, significant changes in MAP and CO were observed during higher infusion rates in groups Bup and Bup+Lid. Q_{LAD} began to decrease at an infusion rate of 4 ml h^{-1}.

SS decreased in a dose-dependent manner during intra-coronary infusion of local anaesthetics (fig. 2). The IR_{50} for group Lid (5.83 (0.87) ml h^{-1}) was significantly less than those for groups Bup and Bup+Lid (2.43 (0.43) and 3.54 (0.56) ml h^{-1}, respectively). There was no difference in IR_{50} between groups Bup and Bup+Lid.

Discussion

As the anaesthetic potency of 0.25% bupivacaine is the same as that of 1% lidocaine, a 1% lidocaine with 0.25% bupivacaine solution is twice as potent as a 0.25% bupivacaine solution. Nevertheless, higher infusion rates of the bupivacaine with lidocaine solution were needed for induction of VF compared with those of the bupivacaine solution. Furthermore, the QRS interval in group Bup was widened at an infusion rate of 4 ml h^{-1} compared with baseline values, whereas that of group Bup+Lid did not differ between baseline and an infusion rate of 4 ml h^{-1}. These *in vivo* findings indicate that the threshold for bupivacaine-induced VF was increased and conduction abnormality attenuated in the presence of lidocaine. Therefore, we have confirmed the extended modulated receptor hypothesis *in vivo*. It is speculated therefore that in the event of accidental intravascular injection during regional anaesthesia, the use of a mixture of lidocaine and bupivacaine would result in less conduction abnormality and less chance of VF than would occur with a bupivacaine solution.

However, we did not find any direct evidence to support treatment against bupivacaine-induced cardiotoxicity with lidocaine, because a mixture of bupivacaine and lidocaine was used in this study. Interestingly, it has been reported that lidocaine was effective in conduction abnormality induced by propoxyphene, the major metabolite of which has slow unbinding kinetics with myocardial sodium channels.[9] The accompanying experiment using rabbit atrial myocytes demonstrated that the recovery time for sodium channel block was shortened from 14.3 (2.9) s during exposure to propoxyphene alone to 1.6 (0.9) s during exposure to a lidocaine and propoxyphene mixture. de Jong and Davis[10] reported that lidocaine converted refractory arrhythmias after bupivacaine overdose in cats undergoing ventilation. Based on these reports, we believe that sodium channel block is attenuated, even if lidocaine is administered by the same mechanism, during bupivacaine-induced cardiotoxicity. However, it must be noted that administration of lidocaine has a limitation, because VF occurred in group Bup+Lid at higher infusion rates. Therefore, further studies are necessary to define the limit of lidocaine treatment against bupivacaine-induced cardiotoxicity.

According to the modulated receptor hypothesis, shortening of action potential duration, decreasing heart rate and induction of diastolic hyperpolarization during diastole are thought to effectively minimize accumulation of sodium channel block with bupivacaine.[5] In fact, potassium channel openers have been shown to attenuate atrioventricular block produced by bupivacaine in isolated guinea pig hearts, presumably by shortening of action potential duration and hyperpolarization.[11] These measures are, however, not feasible during routine clinical practice because of their myocardial depressant effects.

Although many drugs, such as magnesium,[12] clonidine,[13] and hexamethonium,[14] have been reported to have a beneficial effect on bupivacaine-induced arrhythmias in experimental studies, their mechanisms have remained speculative. More importantly, these drugs have not been reported to be clinically effective. Epinephrine is often added to local anaesthetics to prevent rapid vascular absorption and to prolong duration of block. It does not, however, protect against bupivacaine-induced cardiotoxicity[15] or even potentiate toxicity.[16] This is explained in part by its arrhythmogenic property. Kasten and Martin[17] showed that bretylium, which is an antifibrillatory agent, but not lidocaine, effectively corrected bupivacaine-induced cardiotoxicity. The discrepancy between their results and ours may be explained by the difference in the experimental model. They examined the effect on ventricular tachycardia threshold using burst ventricular pacing instead of the occurrence of actual VF. Moreover, as bretylium prolongs ventricular action potential duration and increases heart rate because of release of catecholamines, it may enhance bupivacaine-induced sodium channel block and therefore worsen cardiotoxicity.

Even at the highest infusion rate, lidocaine did not cause QRS widening. Moreover, no animal in group Lid died of VF despite a high mean venous plasma concentration of 58.3 (6.7) μg ml^{-1}. This may suggest a greater margin of safety against VF during lidocaine-induced cardiotoxicity. This is consistent with previous reports in sheep by Nancarrow and colleagues.[18] They reported that respiratory depression and hypotension were the causes of death in lidocaine-treated sheep, whereas three of four bupivacaine-treated sheep died after sudden onset of VF or ventricular tachycardia.

The dose–response relationship for SS revealed no difference between groups Bup and Bup+Lid, although SS decreased with increase in infusion rate of local anaesthetics in the three groups. This indicates that inclusion of lidocaine at the same potency did not increase bupivacaine-induced depression of myocardial contractility. In support of these findings, de Jong and Davis showed that hypotension was not precipitated by lidocaine in cats after bupivacaine-induced cardiotoxicity.[10] There were also no significant differences in Q_{LAD}, HR, MAP or CO between groups Bup+Lid and Bup. We conclude that the combined use of lidocaine and bupivacaine is not associated with further depression of myocardial contractility.

We used the selective LAD infusion technique in beating hearts in this study. An advantage of our model was that we could evaluate the direct myocardial effects of drugs without interference of other organs. This is important because bupivacaine-induced cardiotoxicity is enhanced by hypoxia and acidosis[19] caused by convulsion or respiratory depression. However, we admit that this model is affected by the re-entry phenomenon in contrast with the clinical situation where the entire heart is exposed to drugs. This may explain why VF occurred without any arrhythmias in this study except for one case of bigeminy, although it is reported that arrhythmias often precede VF during cardiotoxicity induced with i.v. bupivacaine infusion.[20]

It is notable that mean body weight in group Bup was significantly less than those of the other groups. However, we do not believe that this difference affected the results, because plasma concentrations of bupivacaine and lidocaine in the anterior intraventricular vein were similar in groups Bup and Bup+Lid groups and in groups Lid and Bup+Lid at corresponding infusion rates.

In summary, the results of this study demonstrated that lidocaine increased the threshold of bupivacaine-induced VF without enhancing myocardial depression. We therefore recommend that regional anaesthesia with relatively high doses of local anaesthetics be performed with a mixture including lidocaine rather than with bupivacaine alone. Furthermore, the results of this study suggest that lidocaine might be the drug of choice for bupivacaine-induced cardiotoxicity predisposing to VF.

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REVIEW ARTICLE

Anaesthesia for telescopic procedures in the thorax

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Over the past decade, there has been an increase in endoscopic procedures within the thorax for diagnostic and therapeutic purposes. Each has its indications, techniques and complications. However, the one common denominator is that there is always the possibility that thoracotomy may be necessary. Occasionally, particularly if considerable haemorrhage occurs, thoracotomy may be required immediately. Consequently, the clinical examination and investigations should be orientated to this possibility. The medical and theatre staff should be prepared for, and trained to deal with, such an eventuality.

GENERAL PREOPERATIVE CONSIDERATIONS

Patients should undergo a complete evaluation for a full posterolateral thoracotomy. The goal is to define all of the problems and to ascertain if the patient is in the best possible condition. Factors known to increase the risk for patients undergoing thoracic surgery include cigarette smoking, advanced age, coronary artery disease, preoperative weight loss, obesity, poor pulmonary function and duration of anaesthesia.[47]

Cardiac risk is determined by the severity of coronary artery disease, presence of cardiac arrhythmias, left ventricular dysfunction, age and associated medical conditions such as hypoxaemia, diabetes and renal insufficiency.[28] An exercise stress test should be performed as patients with ischaemia are at a higher risk of perioperative cardiac complications and death when undergoing major operations such as pneumonectomy.[22] Consideration should be given to cardiac catheterization and, if appropriate, coronary artery bypass grafting before major lung resection. However, it is not known if this is true for patients undergoing thoracoscopic pulmonary resection.

The preoperative evaluation of the respiratory system involves taking a history, physical examination, exercise tolerance, routine laboratory tests, including arterial blood-gas tensions, radiography and pulmonary function tests. Patients who show an increase in peak expiratory flow rate by 15% or more after administration of bronchodilators should receive perioperative bronchodilators. A forced vital capacity (FVC) of at least three times the tidal volume is necessary for an effective cough and a value of less than 50% of predicted is an indicator of increased risk of postoperative ventilator dependency.[31] A maximum voluntary ventilation less than 50% of predicted is another poor prognostic indicator and indicates possible postoperative atelectasis and infection.[12] In patients with marginal pulmonary function who are considered for lung resection, a quantitative ventilation–perfusion scan is indicated. The percent of perfusion delivered to the lung which is to be resected is multiplied by the preoperative FVC or forced vital capacity in 1 s (FEV_1). Patients who have a predicted postoperative FEV_1 of less than 800 ml are generally considered a prohibitive operative risk. At least 2 u. of blood should normally be available. However, grouping and saving of serum should be sufficient cover for bronchoscopy.

Bronchoscopy

Bronchoscopy is the oldest and most frequently performed endoscopic procedure used in the assessment and management of patients with pathology in the thoracic cavity. It may be rigid or flexible. The first rigid bronchoscopy was performed by Gustav Hillian in 1897. The technique was developed by Chevalier Jackson in the USA and by Victor Negus in the UK in the early years of the 20th century. The flexible fibreoptic bronchoscope was introduced into clinical practice by Shigeto Ikeda in 1968.

The roles of rigid and flexible fibreoptic bronchoscopy in current clinical practice have been reviewed.[25] Although rigid bronchoscopy has generally been superseded by flexible fibreoptic bronchoscopy for the initial assessment of airway and thoracic disease, it remains the procedure of choice for surgical assessment before staging procedures such as mediastinoscopy and before thoracotomy. The rigid bronchoscope is also the preferred instrument for use in small children, in adults with massive haemoptysis and for therapeutic procedures such as foreign body removal, stent insertion and endoscopic resection of airway tumours.

PREOPERATIVE ASSESSMENT

A full history and clinical examination are essential. Patients who require bronchoscopy are frequently cigarette smokers with hyper-reactive airway reflexes and are likely to have impaired cardiovascular and

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respiratory function. Preoperative assessment should be directed to the identification of such patients and to optimal control of co-existing medical conditions.

Preoperative investigations should include routine haematology and biochemistry, a 12-lead electrocardiograph in adults and a chest radiograph in all patients. More advanced imaging of the chest, such as computerized tomography or magnetic resonance scanning, in addition to pulmonary function tests and arterial blood-gas analysis may also be appropriate. If bronchoscopy is to be performed immediately before thoracotomy, such investigations are mandatory.

The chest radiograph is particularly important as it demonstrates areas of pulmonary collapse and consolidation, and highlights the presence of an air-filled cavity such as a lung bulla or a pneumothorax. In a patient who has inhaled a foreign body, chest radiographs performed at the end of inspiration and expiration may reveal an emphysematous area distal to the site of the foreign body. This indicates that the foreign body is acting as a "ball valve" in the lower airway, allowing air entry during inspiration but preventing the exit of the same volume of air during expiration. This radiographic finding contraindicates the use of nitrous oxide and positive pressure ventilation during general anaesthesia as a consequence of their potential to increase the size of an air-filled cavity, which may result in both respiratory and cardiovascular embarrassment. This is particularly important in children

PREMEDICATION

Premedication should include the patient's regular cardiovascular and respiratory medications. Diabetic patients should omit their usual oral antidiabetic medication. Those who are insulin-dependent should be managed using an i.v. glucose–insulin regimen. Particular attention should be paid to the preoperative control of bronchospasm as perioperative morbidity and mortality are particularly high in such patients.[51]

A short-acting benzodiazepine may be administered to relieve preoperative anxiety without delaying recovery of consciousness at the end of the procedure. Sedative agents should, however, be avoided in the presence of upper airway obstruction. An anticholinergic agent may be administered to counter the muscarinic effects of the anaesthetic drugs to be used and the surgical procedure.

MONITORING

Minimum monitoring is essential for both flexible fibreoptic and rigid bronchoscopy, whether the procedure is to be performed with sedation and local anaesthesia or with general anaesthesia, as cardiovascular and respiratory complications are common.[51] Minimum monitoring should comprise an electrocardiograph, an intermittent non-invasive method to measure arterial pressure and continuous pulse oximetry to measure arterial oxygen saturation. Capnography should also be used during flexible fibreoptic bronchoscopy under general anaesthesia, but is not easily adapted for use with the unsealed airway during rigid bronchoscopy. Monitoring should always be attached before administration of sedative or anaesthetic agents and continued until the patient has recovered fully from the procedure. In future, the use of transcutaneous carbon dioxide monitoring may be an appropriate alternative, particularly in children and during prolonged procedures.

FLEXIBLE FIBREOPTIC BRONCHOSCOPY

The flexible fibreoptic bronchoscope is available in varying sizes for use both in children and adults. Passage of the bronchoscope via the nose or mouth is a relatively atraumatic procedure and can be performed under sedation and topical anaesthesia in the majority of patients. General anaesthesia is reserved for children and those adults who are unable to tolerate the procedure awake.

Sedation is usually provided by a combination of a benzodiazepine and an opioid. Propofol by continuous infusion may also be used safely as a sedative for flexible fibreoptic bronchoscopy.[20] If passage of the bronchoscope via the nose is required, the nasal mucosa can be anaesthetized using either cocaine or one of the newer local anaesthetic agents in combination with a vasoconstrictor. A detailed description of the methods available to produce topical anaesthesia of the lower respiratory tract is beyond the scope of this review. In practice, local anaesthetic agents may be effectively administered by nebulization, cricothyroid puncture or using a "spray as you go" technique.[42] Large doses of local anaesthetic agents are required for effective topical anaesthesia. Systemic absorption resulting in local anaesthetic toxicity is a significant risk.[44]

In the anaesthetized patient, the flexible fibreoptic bronchoscope is usually introduced into the trachea via a self-sealing diaphragm in the angle piece attached to a tracheal tube. Ventilation of the lungs with an anaesthetic gas mixture of known concentration can be continued around the outside of the bronchoscope but within the lumen of the tracheal tube. The presence of the bronchoscope within the tracheal tube reduces the available internal cross-sectional area and increases resistance to the flow of gas via the tracheal tube. Consequently, it is important to use the largest feasible tracheal tube in each individual patient. It is also usual to administer neuromuscular blocking agents and to control ventilation, a technique which has been shown to maintain satisfactory gas exchange.[49]

The laryngeal mask airway (LMA) has also been used as a conduit for the flexible fibreoptic bronchoscope in both awake and anaesthetized patients.[5 13] Although the internal cross-sectional area of the shaft of the laryngeal mask airway is greater than that of a corresponding tracheal tube, consideration should be given to the increase in resistance to gas flow produced by insertion of the bronchoscope and the requirement for controlled ventilation.

An alternative approach involves the passage of the flexible bronchoscope into the upper airway of a spontaneously breathing patient via either the diaphragm of an angle piece attached to an anaesthetic face mask,[46] or via a second aperture on a modified face mask, such as the Patil Syracuse mask.[63] This technique avoids the problem of a reduced space for ventilation between the internal

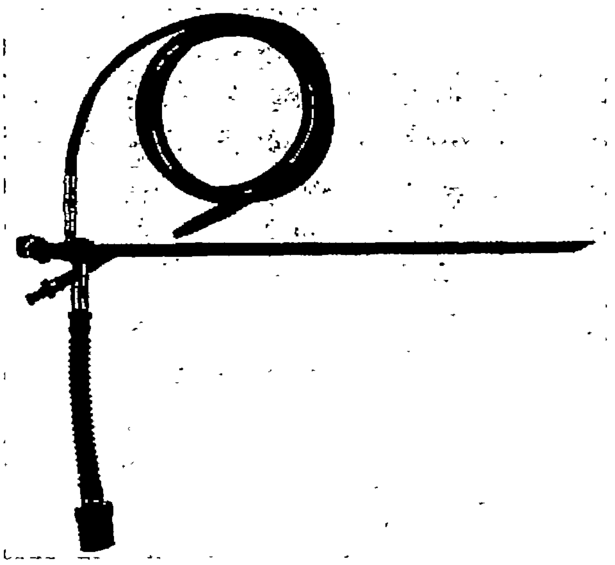

Figure 1 The Storz bronchoscope with a standard breathing system.

wall of the tracheal tube or laryngeal mask airway and the fibreoptic bronchoscope.

RIGID BRONCHOSCOPE

The original rigid bronchoscopes were open-ended, tapered metallic tubes, available in a variety of sizes. Side-holes down the body of the bronchoscope were incorporated later to allow bilateral lung ventilation when the tip of the bronchoscope was in one of the major bronchi. Further modifications to this basic design led to the development of the rigid ventilating bronchoscopes used in current practice which can use a breathing system or a Venturi system to achieve ventilation.

The rigid ventilating bronchoscope incorporates a sidearm adapter which can be attached to an anaesthetic breathing system (fig. 1). Occlusion of the proximal end of the bronchoscope by an eyepiece allows spontaneous or controlled ventilation to occur through the lumen of the bronchoscope. There is a variable gas leak around the bronchoscope.

The rigid bronchoscope which uses the Venturi principle incorporates a needle within its lumen and runs parallel to its long axis (fig. 2). Release of gas from a high pressure source via the needle entrains environmental gas through the proximal open end of the bronchoscope and allows controlled ventilation to occur through the lumen of the bronchoscope.

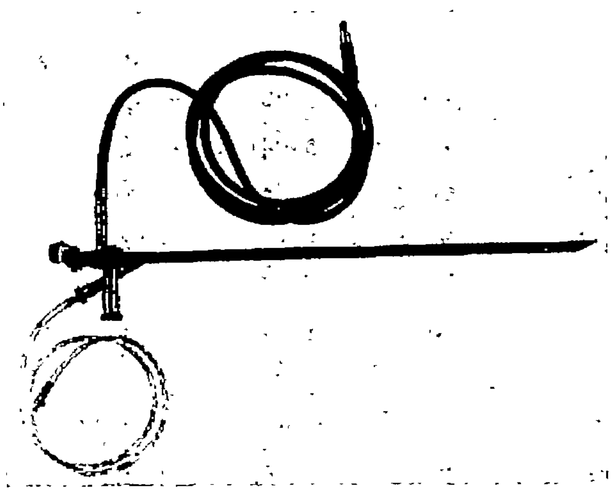

Figure 2 The Storz bronchoscope with the Sanders injector.

In contrast with flexible fibreoptic bronchoscopy, rigid bronchoscopy produces a considerable amount of mucosal stimulation, pressure on soft tissues and requires significant extension of the cervical spine. Consequently, this procedure is almost always performed under general anaesthesia. In children, it is advisable that a laryngoscope is used to expose the vocal cords which may also be sprayed with local anaesthetic solution. Such exposure also allows the endoscopist to introduce the correct size bronchoscope with minimum delay and reduces the chances of trauma to the cords.

Patients are able to breathe or their lungs can be ventilated around the flexible fibreoptic bronchoscope. In contrast, the rigid bronchoscope is hollow and patients must either breathe or undergo ventilation through it. The performance of rigid bronchoscopy under general anaesthesia therefore requires that the responsibility for the management of the airway be shared between the anaesthetist and the endoscopist. The anaesthetist must maintain adequate oxygenation and carbon dioxide elimination during a procedure that inevitably interferes with airway and respiratory function.

ANAESTHETIC TECHNIQUES

Rigid bronchoscopy can be performed in the spontaneously breathing patient under a deep plane of anaesthesia using an inhalation anaesthetic agent. This remains a popular technique in some centres for children and for adults with upper airway obstruction. Meretoja and colleagues have recently compared sevoflurane in oxygen and nitrous oxide with halothane in oxygen and nitrous oxide for induction and maintenance of anaesthesia in infants and children undergoing rigid bronchoscopy or gastroscopy.[56] In the sevoflurane group, induction and recovery times were shorter and there were significantly fewer complications, particularly arrhythmias and laryngeal spasm.

Complications of performing rigid bronchoscopy in spontaneously breathing patients range from laryngeal spasm and bronchospasm caused by inadequate anaesthesia, to hypoventilation as a result of excessive anaesthesia. As a consequence, it is common practice to administer an i.v. anaesthetic agent, a neuromuscular blocking agent and to use intermittent positive pressure ventilation. Anaesthesia is maintained by administration of either an inhalation agent, increasingly sevoflurane or an i.v. anaesthetic agent, increasingly propofol. As the inspired oxygen and inhalation anaesthetic agent concentrations are known with a ventilating bronchoscope but not known using the Venturi system bronchoscope, rigid ventilating bronchoscopy can be performed with either inhalation or i.v. anaesthesia. However, rigid bronchoscopy using the Venturi system is best performed under total i.v. anaesthesia using an $F\text{I}_{O_2}$ of 1.0. Intermittent bolus doses of methohexital, etomidate, thiopental and propofol have been used for this purpose.[38 53 82] The problems of using these i.v. techniques include awareness caused by administration of inadequate increments of anaesthetic agent and delayed recovery as a result of administration of excessive anaesthetic agent.[3,21] It is preferable, therefore, for all but the shortest procedures, to administer the i.v. anaesthetic agent by continuous infusion. Alfentanil followed by infusion of propofol has been shown to provide satisfactory anaesthesia for bronchoscopy without awareness during the procedure, with a rapid postoperative recovery.[45]

The haemodynamic responses to rigid bronchoscopy have been the subject of several studies. These responses are qualitatively similar to the responses caused by direct laryngoscopy and tracheal intubation, but may be of greater magnitude and longer duration.[82] Significant increases in heart rate, systolic and diastolic arterial pressures follow rigid bronchoscopy after thiopental but not propofol anaesthesia.[58] Myocardial ischaemia may occur during general anaesthesia for rigid bronchoscopy with or without the development of significant haemodynamic abnormalities.[58,82] The addition of a small dose of an i.v. opioid partially controls the haemodynamic responses caused by rigid bronchoscopy after thiopental but is superfluous after propofol.[3,58] Others use the ultra-short-acting β blocker esmolol to attenuate the responses to both bronchoscopy and endobronchial intubation.[74,80] There is no evidence that the use of anticholinergic agents to control airway secretions aggravates the haemodynamic response to rigid bronchoscopy.[33,52]

Neuromuscular block for rigid bronchoscopy may be produced by a variety of agents. The choice is determined by the anticipated duration of the procedure. The depolarizing agent succinylcholine remains popular for short procedures, although the short-acting non-depolarizing agent mivacurium is a suitable alternative. If bronchoscopy is expected to be prolonged or is to be followed by a surgical procedure, a longer acting non-depolarizing neuromuscular blocking agent may be used.

Administration of a local anaesthetic agent to the vocal cords and trachea before rigid bronchoscopy under general anaesthesia has been recommended to prevent laryngeal spasm after the bronchoscope is removed.[19] However, the only study of this practice did not demonstrate any advantage when 4% lignocaine 4 ml was sprayed onto the larynx before bronchoscopy.[1] Furthermore, the associated depression of the cough reflex is undesirable, particularly when excessive secretions or haemorrhage develop after bronchoscopy.

Gas exchange in the anaesthetized and paralysed patient may be produced using a variety of methods: (1) apnoeic oxygenation; (2) rigid ventilating bronchoscopy; (3) rigid bronchoscopy with Venturi attachment; (4) high frequency jet ventilation; and (5) use of the Hayek oscillator

(1) Apnoeic oxygenation

Insufflation of oxygen via a catheter placed into the lower trachea is a satisfactory method of maintaining oxygenation in a patient who has been preoxygenated, anaesthetized and paralysed for rigid bronchoscopy.[17,29] The technique is limited by the development of progressive hypercapnia and respiratory acidosis, Pa_{CO_2} increasing at a rate of 0.5 kPa (3–5 mm Hg) per minute.[23,29,84]

(2) Rigid ventilating bronchoscope

The rigid ventilating bronchoscope was developed to provide conditions similar to tracheal intubation.[57,69] It incorporates at its proximal end a side port which can be attached to an anaesthetic breathing system, allowing continuous flow of anaesthetic gases and vapours. Occlusion of the proximal end of the bronchoscope by a sliding eyepiece allows spontaneous or controlled ventilation to occur via the lumen of the bronchoscope. There is a variable flow of gas around the distal end of the bronchoscope, compensated for by providing a high fresh gas flow or by packing the laryngopharynx.

The major disadvantage of the rigid ventilating bronchoscope is that the sliding eyepiece must be removed during surgical manoeuvres such as suctioning or obtaining biopsy specimens. These interruptions to ventilation inevitably result in progressive hypercapnia and respiratory acidosis when the rigid ventilating bronchoscope is used in the anaesthetized, paralysed patient.[32,58] Pollution is also a problem as scavenging is almost impossible with this system.

(3) Rigid bronchoscope using the Venturi principle

The first rigid bronchoscope using the Venturi principle was described by Sanders in 1967.[70] He developed an attachment applied to the proximal end of an open bronchoscope which used the energy of compressed oxygen exerted through an injection needle placed inside and running parallel to the long axis of the bronchoscope. Environmental air was entrained by the Venturi effect and generated a pressure within the bronchoscope sufficient to inflate the lungs with a variable oxygen–air mixture. A pressure regulator was required to maintain a constant pressure and the flow was controlled by a manually operated on–off valve placed in the line connecting the pressure regulator to the attachment. Uninterrupted controlled ventilation could be achieved without occlusion of the open end of the bronchoscope and without interference with vision or instrumentation through the bronchoscope. Sanders stated that the use of this device maintained oxygenation without producing hypercapnia and respiratory acidosis. This was subsequently confirmed by several detailed studies.[32,64,71]

Spoerel and Grant established that the pressure produced at the distal end of the bronchoscope by the Sanders device varied with the volume of oxygen flow into the bronchoscope. This is determined by the driving pressure from the reducing valve, the size of the injector needle, and the diameter, length and type of bronchoscope.[73] The tidal volumes generated in an individual are thus dependent on the pressure produced at the distal end of the bronchoscope, the size of the leak around the bronchoscope and compliance of the lungs.

To avoid lung barotrauma, it is important to match the volume of oxygen flow into the bronchoscope to the diameter, length and type of bronchoscope in use. This may be achieved by altering either the driving pressure or the size of the injector needle. In practice, it is usual to maintain a constant driving pressure and adjust the size of the injector needle.

Bethune and colleagues determined the maximum pressures generated in the Negus range of bronchoscopes with varying sizes of injector needle and a driving pressure equal to the standard oxygen pipeline pressure of 410 kPa. A 16-SWG needle is suitable for adults, a 18-SWG needle for adolescents and a 19-SWG needle for children, infants and neonates.[10] A 14-SWG needle may be required in adults with poor compliance in order to achieve the high inflation pressures necessary to produce adequate tidal ventilation.[9]

Carden, Trapp and Oulton described a modification of the original device in which oxygen was injected through the sidearm of the bronchoscope with little or no air entrainment.[16] Subsequent comparison of this system with the Sanders device has confirmed that the sidearm system delivers much higher oxygen concentrations and therefore, results in high Pa_{O_2} concentrations without producing hypercapnia and respiratory acidosis.[14] This system may also be used to deliver a premixed nitrous oxide–oxygen gas mixture.[15]

It is essential when using any bronchoscope with a Venturi system that the proximal end of the bronchoscope remains open to allow entrainment of air during inspiration and escape of gas during expiration. Otherwise, lung barotrauma may result.

(4) High frequency jet ventilation

The use of high frequency ventilators to produce high frequency–low volume ventilation via the sidearm of the rigid bronchoscope has been shown to achieve suitable operating conditions and adequate gas exchange at rates up to 300 bpm.[79] The technique is popular in some countries, but is not widely used in the UK.

(5) The Hayek oscillator

Rigid bronchoscopy has been performed under general anaesthesia with muscle paralysis and external negative pressure ventilation produced by the Hayek oscillator.[60] There would appear to be no detriment to gas exchange in the lungs. In addition, the endoscopist had total freedom for the investigation as there are no attachments to the bronchoscope whatsoever. This arrangement would also be of benefit during laser therapy to the respiratory tract.

POSTOPERATIVE CARE

At the end of the procedure, administration of anaesthetic agents should be discontinued, 100% oxygen given and the residual effects of non-depolarizing neuromuscular blocking agents antagonized with an anticholinesterase. If a general anaesthetic has been administered, it is advisable to perform direct laryngoscopy and, if necessary, use a suction catheter to clear secretions, blood or other debris from the upper airway. The bronchoscope is removed from the airway before re-establishing control of the upper airway with either a face mask and oropharyngeal airway, a laryngeal mask airway or insertion of a tracheal tube. In the presence of infection or haemorrhage after a biopsy, the patient should be placed *with the bad lung* down to protect the good lung until the cough reflex returns. The patient should be allowed to recover by breathing a humidified oxygen-enriched air mixture before transfer to a fully monitored recovery area.

COMPLICATIONS

Complications of flexible fibreoptic and rigid bronchoscopy can be classified conveniently into three groups.

Anatomical

Damage to teeth or dental work is not an uncommon occurrence during bronchoscopy. Direct trauma to other structures in the upper and lower airways may result in haemorrhage, oedema or tumour fragmentation which may compromise the airway. Mucosal perforation may lead to subcutaneous emphysema, mediastinal emphysema or tension pneumothoraces.[30] Such complications are particularly likely during bronchoscopic biopsy. An emergency thoracotomy may be required to repair the damage.

Mucosal disruption leading to subcutaneous emphysema, mediastinal emphysema and tension pneumothoracies may also develop as a consequence of barotrauma.[62] Lung barotrauma is particularly likely to occur if a bronchoscope using a Venturi attachment is used carelessly, especially in children, where the escape of gas around the bronchoscope is limited because of a tight fit of the bronchoscope in the glottis.

Physiological

Arrhythmias are frequent during bronchoscopy.[51] Bradycardia occurs as a vagally mediated response to insertion of the bronchoscope and may necessitate i.v. administration of an anticholinergic agent. Other arrhythmias are the result of catecholamines produced in response to the surgical stimulus. Hypoxia and hypercapnia may contribute to these arrhythmias and should be corrected before specific antiarrhythmics are administered.

After extubation

The development of upper airway obstruction may complicate the recovery period. The commonest causes are laryngeal spasm, masseter spasm or laryngeal oedema . Management of these complications has been reviewed recently,[34] and algorithms have been proposed for their treatment.[34 76]

Mediastinoscopy

Mediastinoscopy, originally described by Carlens in 1959,[11] is performed for two major reasons: first, to obtain tissue for histological diagnosis, and second, to stage lung malignancy. A histological diagnosis is very important as a lymphoma is treated with radiation while a thymoma, for example, requires resection. A diagnosis of tuberculosis or sarcoidosis will also lead to correct treatment.

The majority of mediastinoscopies are performed via the neck, entering the mediastinum behind the manubrium—the so-called cervical mediastinoscopy. The second, and less common approach, is through the second left interspace (the anterior approach) to inspect the lower left mediastinum.[40] The former approach is more difficult and has a greater complication rate for several reasons.

- Compression of the trachea and major blood vessels by the mediastinoscope, particularly on the right side. This may lead to a decrease in both venous return and flow to the right carotid and subclavian arteries.
- Torrential haemorrhage from biopsy sites which can lead to acute exsanguination requiring emergency thoracotomy.[77] The main reason for such an event is that as the mediastinal glands enlarge, blood vessels become stretched over them and can appear as an integral part of the mass. Biopsy can cause blood vessels to divide, the cut ends part and bleed profusely into the mediastinum. Furthermore, it may prove difficult to replace blood loss from cannulation sites in the arms and upper body as any fluids used during resuscitation pour into the mediastinum. Hence, it is mandatory to have: two large venous cannulae, one in the arm and the other in the leg; and at least 2 u. of crossed matched blood in theatre before the operation commences.

Other complications that may arise from either approach have been summarized by Benumof[5] (table 1).

PREOPERATIVE ASSESSMENT

The anaesthetic management of patients presenting for mediastinoscopy depends on the clinical condition and awareness of possible anaesthetic and surgical complications. These patients can present with a variety of symptoms.

- None: a mass had been noticed on routine chest x-ray.
- Dyspnoea: this symptom has increased over the past few months. These patients feel increasingly uncomfortable if they lie flat.
- Superior vena cave obstruction: this can present as dyspnoea, fullness of the face, ankle swelling and as a bluish colour of the upper part of the body. These patients have great difficulty in lying flat.
- Dry cough and possible stridor: these may be indications of tracheal involvement.
- Increasing muscle weakness: this may be associated with a thymoma and possibly a myasthenic syndrome.

The preoperative clinical assessment enables the anaesthetist to obtain these relevant symptoms. Standard haematological and biochemistry investigations in additon to arterial blood-gas tensions and basic lungs function tests should be available. Computed tomographical scans of the neck, thoracic inlet and chest have superseded the older imaging techniques.

Table 1 Major complications of mediastinoscopy (by kind permission of J. L. Benumof)

- Haemorrhage
- Pneumothorax
  - Recurrent laryngeal nerve injury
  - Air embolism
  - Compression of vessels
    - a. Aorta → reflex bradycardia
    - b. Innominate artery
    - Right carotid → hemiparesis
    - Right subclavian → loss of right radial pulse
  - Compression of trachea
  - Infection, tumour spread

PREMEDICATION

A variety of premedications have been used with few adverse effects, although light oral premedication with a benzodiazepine is currently favoured. No premedication is given in the presence of tracheal compression.

ANAESTHETIC TECHNIQUES

Mediastinoscopy can be performed under sedation and local analgesia but this is generally no longer practised.[59]

The ideal general anaesthetic should produce profound depression of laryngeal and tracheal reflexes followed by rapid recovery. Whichever technique is used, it is essential that minimum monitoring is established. The arterial pressure cuff however, is always applied to the right arm. The right radial artery can also be cannulated under local anaesthesia to provide a continuous display of arterial pressure. Thereafter, the techniques depend on the clinical condition.

Mediastinoscopy in a patient with no symptoms or signs

Preoxygenation is followed by i.v. induction using propofol. A short-acting neuromuscular blocking agent such as vecuronium is given. The cords may be sprayed with lidocaine and the anaesthetist intubates the trachea with a reinforced tracheal tube. A short-acting opioid such as alfentanil can be used.

Mediastinoscopy in the presence of venous congestion

A similar technique can be used but the inflation pressures required to ventilate the patient's lungs should be kept to the minimum to prevent further undue decreases in venous return. I.v. opioids are best avoided.

Mediastinoscopy in the presence of respiratory obstruction, myasthenic syndrome, or both

An awake intubation under local anaesthesia is the technique of choice. Alternatively, inhalation induction is used and a reinforced tube introduced into the trachea under deep anaesthesia after the vocal cords have been sprayed with a local anaesthetic agent. An opioid is contraindicated.

MAINTENANCE

The use of non-depolarizing neuromuscular blocking agents is generally considered essential as the preferred maintenance technique involves intermittent positive pressure ventilation using oxygen, nitrous oxide and a volatile agent. Furthermore, non-depolarizing agents such as vecuronium and atracurium have been used in the presence of myasthenia gravis provided the doses are reduced and neuromuscular activity is monitored using the train-of-four sequence.[41] In the future, sevoflurane and remifentanil will possibly be the drugs of choice because of their rapid onset of anaesthesia and rapid recovery. The patient is placed in a slight head-up position to try and reduce congestion in the great veins. Before the start of the surgical procedure, a large venous cannula should be established in the lower limbs.

MONITORING

Minimum monitoring is used but arterial pressure in the right arm must be constantly measured for two reasons: (1) to note any compression of the right common carotid artery; and (2) to note any decline in pressure associated with possible blood loss.

The gauge on the ventilator must also be noted for two reasons: (1) to use the lowest pressures compatible with high saturation and normal end-tidal carbon dioxide; (2) to note any acute increases in pressure which are usually associated with tracheal compression.

If compression of either the trachea or vasculature occurs, the surgeon must be informed immediately and told to either remove or reposition the mediastinoscope.

COMPLICATIONS

The most serious complication is haemorrhage after a perforated vessel. This can be treated by two methods.

(1) The mediastinum can be packed with swabs soaked in a weak epinephrine solution. Vital signs are monitored constantly. If these remain constant, the swabs are removed after 10 min and the mediastinoscope reintroduced to inspect the damage. If the bleeding has stopped, a drain is left in the mediastinum for at least 24 h.
(2) If the bleeding continues, arterial pressure begins to decrease and heart rate increases, then a thoracotomy is required. It is recommended that a posterolateral approach is used. Under such emergency circumstances it may be ill advised to replace the reinforced tube with a double-lumen endobronchial tube as this may cause undue delay. In addition, blood for resuscitation and replacement may be better infused via the large venous cannula in the lower limb. The tear or hole in the blood vessel is repaired as rapidly as possible.

Air embolism is an important consideration but is extremely rare as most patients are ventilated artificially. If it does occur and is clinically significant, the patient should be placed in the left head-down lateral position and treated accordingly.

POSTOPERATIVE MANAGEMENT

Neuromuscular block is antagonized, 100% oxygen is given and the tracheal tube removed when appropriate. Patients are transferred to the recovery room, breathing oxygen-enriched air. They receive routine monitoring and are sat up as soon as is possible. Those patients who have had a thoracotomy are managed along the lines set out at the end of this review.

Oesophagoscopy

This investigation is performed for three main reasons namely[24]: (1) diagnosis, particularly of carcinoma; (2) removal of a foreign body; and (3) therapeutic, for example injection of oesophageal varices or dilatation of a stricture. Very rarely, it is performed to identify the origin of an oesophageal pouch.

The major problems associated with this investigation are: fluids, blood and solids proximal to the lesion; possible regurgitation of stomach contents; and perforation of the oesophagus.

PREOPERATIVE PREPARATION

Many of the patients are elderly, with the additional problems of multiple treatments (e.g. digoxin and diuretics). Furthermore, some of these patients may be dehydrated as a result of dysphagia, and rehydration is required. Recently, however, preoperative chemotherapy has usually enabled many of these patients to be able to swallow and to return to a normal fluid and electrolyte balance.

PREMEDICATION

It is inadvisable to administer oral premedication. The main reasons are that the drugs may stay in the oesophagus proximal to the lesion and cause retching. Premedication is therefore either avoided or given i.m. Because of possible difficulties in swallowing, antacids are rarely used. However, there are reasonable grounds for using i.v. agents which reduce gastric secretions and increase gastric emptying.

INDUCTION

The investigation can be performed under sedation and local analgesia or general anaesthesia.[66] Minimum monitoring is mandatory for each procedure.

Sedation and local analgesia

There are a variety of techniques available. Most use i.v. sedation (e.g. midazolam) and topical analgesia to the upper respiratory and oesophageal tracts. A fibreoptic oesophagoscope is generally used for inspection and therapeutic procedures. The safety of such procedures has been addressed.[66 67] However, the fibrescope cannot be used to remove foreign bodies or in children.

General anaesthesia

Several agents have been used to induce anaesthesia after a suitable period of preoxygenation. A rapid sequence technique is used with succinylcholine and cricothyroid pressure. The trachea is intubated with a reinforced tube which is moved to the left side of the mouth to permit passage of either a rigid or flexible oesophagoscope. The rigid variety can compress a standard tracheal tube. Most anaesthetists do not wait for the action of succinylcholine to "wear off" before giving a short acting non-depolarizing neuromuscular blocking agent. The reason for this approach is that coughing can increase the chances of the major complication of this procedure namely, oesophageal perforation. Inflation pressures are monitored continuously but additional vigilance is required in children during oesophagoscopy as there are no suitably sized reinforced tracheal tubes available. On rare occasions, when an oesophageal pouch is present, a CT scan is mandatory so that the anaesthetist can position the patient appropriately before induction. The patient is placed in either the left or right semi-lateral positions with the pouch of the sac lowermost. Occasionally, a full lateral position is required. The object is to contain any fluid or solids in the sac until intubation has been accomplished. Cricothyroid pressure is not effective in containing the contents in the sac. Indeed, some may argue that the manoeuvre itself may compress the sac and cause the contents to enter the pharynx.[78]

MAINTENANCE

Anaesthesia is usually maintained with oxygen, nitrous oxide and a volatile agent using intermittent position pressure ventilation. Continuous i.v. propofol is also an acceptable technique. The use of i.v. opioids is optional. Two key monitors are: (1) the ECG, which can show the occasional arrhythmia which is generally not significant; and (2) inflation pressures, which must be monitored continuously to detect compression of the tracheal tube.

POSTOPERATIVE MANAGEMENT

Neuromuscular block is antagonized and 100% oxygen is administered until spontaneous ventilation returns. The trachea is normally extubated in the head-down left lateral position. Patients are transferred to the recovery room breathing oxygen-enriched air. A chest x-ray is always obtained to ensure that there has been no oesophageal perforation. Most surgeons do not allow their patients to drink any fluids for 12 h, some even for 24 h, and maintain hydration by the i.v. route.

Thoracoscopy

PRINCIPLES

The first series of thoracoscopy cases were reported in 1921. The Swedish physician, Jacobaeus, used the technique to treat pulmonary tuberculosis and pleural effusions.[43] The development of antibiotics to treat tuberculosis led to virtual cessation of thoracoscopic procedures. Recent advances in endoscopic surgical equipment and refinement of surgical techniques have expanded the role of thoracoscopy to include multiple procedures that previously could only be performed by open thoracotomy.[18 48 57 75 81] The major cause of morbidity after thoracotomy is the incision and associated spreading of the ribs even in limited and muscle-sparing procedures.[36]

Thoracoscopy provides access to the thoracic cavity, is associated with reduced morbidity and does not appear to compromise the procedure.[54] Subsequent studies have confirmed reduced postoperative pain, faster recovery to preoperative functional status and reduced hospital stay after procedures ranging from lung biopsy to lobectomy.[26 50 61 68 83]

Thoracoscopic procedures are currently used to aid the diagnoses of pleural, lung and oesophageal disease, and to assess the extent of lung trauma. Therapeutic uses include lung resection, laser ablation of emphysematous bullae, oesophageal resection, pericardectomy, sympathectomy, removal of mediastinal masses and some spinal surgery. The anaesthetist is therefore faced with establishing one-lung anaesthesia, the associated complications and the potential for a "minimally invasive", but often lengthy, procedure, which may be rapidly converted into an open thoracotomy.

PATIENT CHARACTERISTICS

It is often high-risk patients who are referred for thoracoscopy with the assumption that the procedure produces less physiological trespass. Barker and colleagues[2] anaesthetized 40 such patients for thoracoscopic laser ablation of emphysematous bullae. The patients were elderly smokers with a high incidence of cardiovascular disease who were "respiratory cripples" with little or no exercise tolerance. They tolerated one-lung ventilation better than expected and had stable haemodynamics. However, they did not have prolonged perioperative courses.

PREOPERATIVE PREPARATION

Preoperative preparation involves stopping smoking, hydration, chest physiotherapy, bronchodilators, antibiotics and possibly steroids. Instruction in the use of incentive spirometry and psychological reassurance are also important, in addition to information on possible methods of postoperative analgesia, such as patient-controlled analgesia. The possibility of proceeding to a thoracotomy should be discussed. Current medications, with the exception of insulin, are continued until the morning of surgery. Benzodiazepines are commonly used to produce anxiolysis and sedation.

MONITORING

The early thoracoscopies were relatively short procedures requiring only brief periods of one-lung ventilation, using basic monitoring. However, as thoracoscopy evolved and became more complex, the procedure has become more similar to thoracotomy in terms of length and duration of one-lung ventilation (OLV). Thus monitoring similar to that used for thoracotomy is routine. This includes ECG, pulse oximetry, arterial cannulation for invasive arterial pressure monitoring and blood-gas sampling. Temperature, peripheral nerve block and end-tidal carbon dioxide monitors should also be used. Procedures used to treat pericardial disease or pericardial tamponade may be augmented by transoesophageal echocardiography. However, there are currently no guidelines for additional monitoring requirements for thoracoscopy, Hartrey, Posskitt and Durkin[35] and Fredman, Oslfanger and Jedeikin[27] reviewed patients undergoing transthoracic endoscopic sympathectomy using one-lung anaesthesia with non-invasive monitoring, and described it as a safe and effective technique. However, their patients were relatively healthy, unlike many patients requiring thoracoscopy, thus highlighting the need to assess each patient individually.

CHOICE OF ANAESTHESIA

Thoracoscopy may be performed under local, regional or general anaesthesia, depending on the proposed procedure, the technical abilities of the anaesthetist and surgeon, and the patient's physical and psychological state. Local anaesthetic infiltration of the lateral thoracic wall and the parietal pleura is the simplest method of providing analgesia. Intercostal nerve or thoracic extradural blocks provide more complete analgesia, supplemented with ipsilateral stellate ganglion block to inhibit the cough reflex stimulated by manipulation of the hilum. Advantages of local techniques are the ability to have an awake, spontaneously breathing patient who is able to cough after operation and has good analgesia. Menzies and Charbonneau[55] showed that diagnostic thoracoscopy for pleural disease under sedation and local anaesthesia was a feasible and safe procedure. The spontaneously breathing patient with an open chest in the lateral decubitus position may have impaired gas exchange as a result of paradoxical respiration and mediastinal shift. It is therefore important to keep the surgical procedure short and simple and always administer supplementary oxygen. General anaesthesia is therefore far more appropriate for most modern thoracoscopies. Intermittent positive pressure ventilation reduces the changes associated with mediastinal shift and prevents paradoxical respiration. It also allows easier monitoring of ventilation. General anaesthesia for thoracoscopy is an indication for the placement of a double-lumen endobronchial tube allowing lung deflation, safe insertion of trocars and provides a better view of the operative side. The lung can be re-expanded under direct vision to assess air leaks or adhesions.

INDUCTION

The anaesthetic technique is tailored to the individual patient. Anaesthesia is induced with either thiopental, etomidate or propofol, and neuromuscular block is provided by vecuronium, atracurium or pancuronium, depending on the proposed length of the procedure. Anaesthesia is maintained with an inhalation agent or continuous infusion of propofol. Opioids can be given to provide analgesia and supplement anaesthesia. Regional and general anaesthesia may be combined to allow a lighter general anaesthetic to be given and to provide postoperative analgesia.

ONE-LUNG ANAESTHESIA

Intermittent positive pressure ventilation in the anaesthetized, paralysed patient with an open chest in the lateral decubitus position can overcome the problems of mediastinal shift and paradoxical respiration encountered in the awake patient. However, there may still be considerable ventilation–perfusion mismatch. Pulmonary blood flow continues to be governed by gravity and changes in resistance in the vasculature, particularly in the non-dependent lung. Ventilation to the dependent lung is reduced because of loss of the dependent lung volume with anaesthesia, compression by mediastinal and abdominal contents, and suboptimal positioning. In addition, poor mucociliary clearance and absorption atelectasis is caused by the increased fraction of inspired oxygen used during one-lung ventilation.

Several techniques are available to achieve one-lung ventilation. The most common uses a double-lumen endobronchial tube (DLT). Many anaesthetists prefer to use left-sided DLT because of the ease of placement and greater margin of safety. Misplacement of a right-sided DLT introduces the risk of inadequate ventilation to the right upper lobe. Fibreoptic bronchoscopy has revealed malpositioning in 48% of cases[72] even though the double-lumen tube was thought to be in the correct position based on clinical signs. When the position of the DLT is confirmed only on the basis of clinical signs, there may be intraoperative problems with either deflating the non-dependent lung or completely separating the two lungs in 25% of the cases.[65] Confirmation of correct position is by fibreoptic brochoscopy[6] after the initial intubation and again when turned into the lateral decubitus position. During one-lung ventilation any blood flow to the non-ventilated lung becomes part of the shunt flow. Consequently, for the same $F\text{I}_{O_2}$, haemodynamic and metabolic status, one-lung ventilation results in a much larger alveolar–arterial oxygen tension difference and lower Pa_{O_2} than two-lung ventilation.

One-lung ventilation has much less effect on Pa_{CO_2} than on Pa_{O_2}. The ventilated lung can eliminate enough carbon dioxide to compensate for the non-ventilated lung. However, it cannot take up enough oxygen because of the plateau at the top end of the oxygen–haemoglobin dissociation curve.

There are both passive and active mechanisms operating during one-lung ventilation that reduce blood flow to the non-dependent, non-ventilated lung. Passive mechanisms include gravity, surgical interference and the extent of pre-existing disease in the non-dependent lung. Hypoxic pulmonary vasoconstriction causes the most dramatic reduction in blood flow to the non-dependent lung by an active vasoconstrictor mechanism. The selective increase in pulmonary vascular resistance of the collapsed lung diverts blood flow towards the remaining ventilated lung.

MANAGEMENT OF ONE-LUNG ANAESTHESIA

One-lung ventilation carries a risk of hypoxaemia. It is therefore important to optimally manage ventilation. $F\text{I}_{O_2}$ should be increased to 0.5 or 1.0 if required to maintain arterial oxygen saturation (Sp_{O_2}) greater than 90%. The benefits of ventilating the dependent lung with 100% oxygen far exceed the theoretical risks of absorption atelectasis and oxygen toxicity. The dependent lung should be ventilated with a tidal volume of approximately 10 ml kg^{-1} with close monitoring of airway pressures. Ventilatory frequency is adjusted to maintain Pa_{CO_2} at 5.3 kPa (40 mm Hg). If there is a problem with ventilation, the correct position of the double-lumen endobronchial tube should be confirmed with the fibreoptic bronchoscope. If hypoxaemia persists, differential lung ventilation should be instituted. Continuous positive airway pressure (CPAP) maintains the patency of the non-dependent lung airways allowing some oxygen distension of the alveolar spaces involved with gas exchange. Because the volume of the ventilated dependent lung is often decreased during one-lung ventilation, many attempts have been made to improve oxygenation by selectively treating this lung with positive end-expiratory pressure (PEEP).

An accepted risk is that PEEP-induced increase in lung volume can cause compression of the intra-alveolar vessels of the small dependent lung and increase pulmonary vascular resistance. Blood flow may then be diverted from the ventilated to the non-ventilated lung, thereby increasing the shunt and decreasing Pa_{O_2}. If oxygenation does not improve with CPAP 5 cm H_2O delivered to the non-dependent lung, PEEP 5 cm H_2O is added to the dependent lung. These pressures can be increased sequentially in search for the maximum compliance and a minimum right-to-left shunt.[7] Resumption of two-lung ventilation is the quickest way to improve oxygenation.

Chest drains are inserted at the end of surgery and connected to underwater drainage systems. In all but the most frail patients, the trachea should be extubated at the end of the procedure and monitored closely in a high dependency unit.

COMPLICATIONS

Haemorrhage is a rare complication of thoracoscopy. Bleeding may be rapid and profuse. Therefore, a large bore venous cannula should be sited before operation. Blood should be available for rapid transfusion. Hypotension may result from cardiac arrythmias, pulmonary embolus or myocardial infarction. Perforation of organs is rare. The anaesthetist should be aware of potential damage to the heart, pericardium, lungs, oesophagus and the sympathetic chain. Occasionally surgeons insufflate the pleural cavity with carbon dioxide via a Verres' needle which increases the risk of perforation of organs and may result in arterial carbon dioxide embolism. Haemodynamic instability is reported by some not to be a problem if the volume of gas is limited to 2 litre and insufflated slowly. However, Hill and colleagues[39] studied haemodynamic changes with positive pressure insufflation of carbon dioxide during OLV in pigs. They demonstrated significant haemodynamic compromise at pressures of 5 mm Hg and greater. A capnothorax has been described in humans which has also demonstrated that there are consequent adverse haemodynamic changes.[69]

Complications related to OLV include hypoxia most commonly caused by malposition of the DLT. During long procedures fluid may collect in the lower lung, particularly if generous i.v. fluids have been given, which further impair gas exchange. Bronchial rupture after over inflation of the bronchial cuff of the DLT is also a rare complication.

When securing the patient in the lateral decubitus position, care must be taken to avoid any nerve injury and to ensure that there is enough room for respiratory excursion. Finally, if laser therapy is used, ventilation with 100% oxygen must be seriously considered as a potential fire hazard.

POSTOPERATIVE MANAGEMENT

Thoracoscopy patients are spared a great deal of postoperative pain and respiratory dysfunction, leading to reduced morbidity and shortened hospital stay. However, these patients still require concerted efforts to minimize complications. A variety of techniques can be used to help reduce postoperative pulmonary complications. Incentive spirometry is an ideal respiratory care manoeuvre. Ensuring the patient sits upright in bed and early ambulation augments the FRC and helps restore a favourable FRC–closing volume relationship thus preventing further atelectasis. Percussion and postural drainage aid in the mobilization of secretions and continuing administration of bronchodilating drugs or steroids that were given before operation is important in maintaining reactive airways quiescent.

Treatment of postoperative pain

Thoracoscopy results in much reduced postoperative pain compared with thoracotomy. Pleural drainage time is also less.[56] Local anaesthetic solutions are often infiltrated into the incisions and pleural cavity, although there is some doubt whether the latter is effective.[8] Post-thoracoscopy pain can be treated by systemic administration of opioid and potent non-steroidal anti-inflammatory drugs.

Parenterally administered analgesics are usually necessary to relieve pain related to chest drains. Patient-controlled analgesia is also an efficient method. Regional analgesia is usually unnecessary in patients who have undergone simple thoracoscopy procedures but provides superior pain relief when used. Extradural analgesia confers the most benefit as it treats both the chest drain and incisional pain, and this improves pulmonary function.

In summary, anaesthesia for surgical telescopic procedures of the thorax has become more refined. Each procedure has certain but different anaesthetic considerations with the one common denominator being that all could be followed by thoracotomy. All medical and nursing staff should be aware of this possibility and be prepared if required to proceed immediately.

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SHORT COMMUNICATIONS

Comparison of intubating conditions after rocuronium or vecuronium when the timing of intubation is judged by clinical criteria

I. SMITH AND R. S. G. SAAD

Summary

The onset of action and intubating conditions after rocuronium 0.6 mg kg^{-1} or vecuronium 0.1 mg kg^{-1} were compared in a randomized, double-blind study when the timing of tracheal intubation was determined by clinical judgment alone. Times to laryngoscopy and completion of intubation were mean 89 (SD 20) s and 119 (28) s, respectively, in the rocuronium group compared with 110 (26) s and 142 (32) s in the vecuronium group (P<0.05 in both cases). Rocuronium also resulted in significantly better intubating conditions compared with vecuronium but with no significant reduction in the haemodynamic response to intubation. We found that onset of satisfactory intubating conditions after rocuronium was detected clinically, although even earlier intubation should be possible by careful timing or by neuromuscular monitoring. (*Br. J. Anaesth.* 1998; **80**: 235–237)

Keywords: neuromuscular block, vecuronium; neuromuscular block, rocuronium; intubation tracheal

Rocuronium is related to vecuronium, but has greater lipophilicity, decreased potency and a faster onset. Good-to-excellent tracheal intubating conditions have been reported[1] within 60–90 s of a 2 × ED$_{95}$ dose of rocuronium 0.6 mg kg^{-1}. In most studies, the timing of tracheal intubation is determined by neuromuscular monitoring or occurs at a predetermined time after administration of neuromuscular blocking drugs. In clinical practice, however, neuromuscular monitoring and accurate timing are rarely used, and many anaesthetists commence laryngoscopy based on the clinical "feel" of the patient. Therefore, we have compared intubating conditions after vecuronium or rocuronium when the timing of laryngoscopy was determined solely by the clinical judgment of an experienced anaesthetist.

Methods and results

After obtaining approval from the local research Ethics Committee and written informed consent, we studied 52 adults undergoing elective inpatient surgery requiring general anaesthesia and tracheal intubation. Patients with neuromuscular disorders, those receiving drugs which might interfere with neuromuscular function and those with anticipated difficult intubation (Mallampati class III or IV)[2] were excluded. Patients were allocated randomly to receive vecuronium 0.1 mg kg^{-1} or rocuronium 0.6 mg kg^{-1}, prepared by an anaesthetist not involved in the study, as a 6-ml solution containing vecuronium 10 mg (1.67 mg ml^{-1}) or rocuronium 60 mg (10 mg ml^{-1}).

Drug administration, airway management and tracheal intubation were the responsibility of an anaesthetist who did not know to which group the patient was allocated. Anaesthesia was induced with propofol 2–2.5 mg kg^{-1} and fentanyl 1 µg kg^{-1}, followed by assisted ventilation with 2% enflurane (inspired concentration) and 60% nitrous oxide in oxygen. After loss of consciousness, neuromuscular block was monitored by acceleromyography[3] with single twitch stimulation at supramaximal, square-wave impulses of 0.2 ms duration, 1 Hz, at the ulnar nerve using a TOF-Guard monitor (Organon Teknika). After calibration to a baseline twitch height of 100%, the display (and the moving thumb) were shielded from the view of the anaesthetist, who injected the neuromuscular blocking drug from the previously prepared syringe at a dose of 0.06 ml kg^{-1} (equivalent to vecuronium 0.1 mg kg^{-1} or rocuronium 0.6 mg kg^{-1}). The timing of laryngoscopy was judged by the ease of ventilation, and jaw and upper airway tone. Jaw tone was assessed by attempting to open the patient's mouth, while upper airway tone was determined by the amount of jaw support necessary to maintain a patent airway. Laryngoscopy was performed with the patient in a standardized position (one pillow) using a size 3 Macintosh laryngoscope blade. Times from administration of neuromuscular blocking drug to beginning laryngoscopy and completion of tracheal intubation, and corresponding values on the neuromuscular monitor were recorded by an assistant. The anaesthetist graded intubating conditions using the Krieg score,[4] ranging from 3 (best possible intubating conditions) to 12 (worst possible conditions). The view at laryngoscopy was also graded: 1=all of the larynx seen; 2=part of the vocal cords seen; 3= epiglottis only seen; 4=no structures identified.[5]

Data were analysed by the Statview statistical package using unpaired t test, chi-square tests and non-parametric tests as appropriate. In all cases P< 0.05 was considered significant.

Data from two patients were excluded because of technical problems with the neuromuscular monitor;

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Table 1 Mallampati classification, times from administration of neuromuscular blocking drug until laryngoscopy and tracheal intubation, with corresponding degrees of neuromuscular block, and view at laryngoscopy in the two groups. Values are mean (SD) [range] or median (range). $^{*}P < 0.05$ compared with vecuronium group

	Vecuronium	Rocuronium
Mallampati class (1/2)	22/3	22/3
Neuromuscular blocking drug to		
Start of laryngoscopy (s)	110 (26) [70–189]	89 (20)* [60–135]
Completion of intubation (s)	142 (32) [106–215]	119 (28)* [68–200]
Twitch height (T1/T0) at		
Start of laryngoscopy (%)	8.0 (0–85)	0 (0–43)*
Completion of intubation (%)	4.0 (0–59)	0 (0–13)*
View at laryngoscopy (*n*)		
1=All of larynx seen	16	15
2=Part of vocal cords seen	9	8
3=Epiglottis only seen	0	2
4=No structures seen	0	0

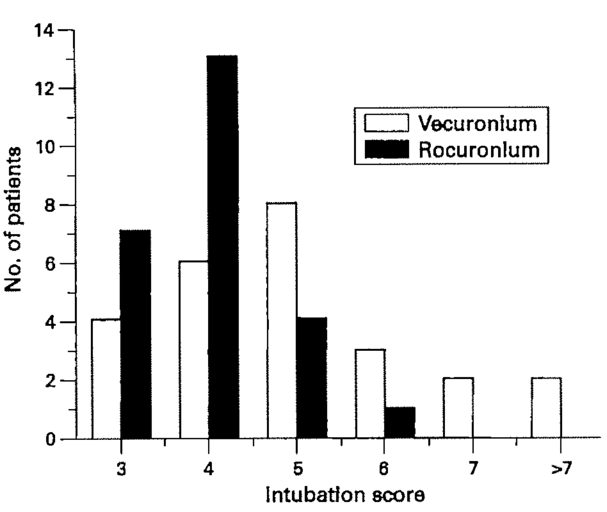

Figure 1 Distribution of intubation scores in patients receiving vecuronium or rocuronium. Scores of 3–4 represent excellent intubating conditions; scores of 5–7 represent good intubating conditions; and scores >7 represent poor conditions.

therefore there were 25 patients in each group. The groups were similar in age, weight, sex, ASA status, Mallampati class, anaesthetic induction dose and time from induction of anaesthesia until administration of neuromuscular blocking drug. In the rocuronium group, laryngoscopy was commenced and tracheal intubation was completed earlier and at a more profound degree of neuromuscular block than in the vecuronium group (table 1). The view at laryngoscopy did not differ significantly between the groups, although two patients in the rocuronium group were grade 3 compared with none in the vecuronium group (table 1). Tracheal intubation was successful at the first attempt in 19 (76%) patients after rocuronium and in 21 (84%) patients after vecuronium. The remaining intubations were completed at the second attempt, except for one patient in the vecuronium group who required three attempts. A bougie was used to facilitate tracheal intubation in four of 25 patients in the rocuronium group (because of anatomical problems) compared with none in the vecuronium group. Nevertheless, intubating conditions were significantly better and intubation scores were significantly lower in the rocuronium compared with the vecuronium group (fig. 1). There were no significant differences between the groups in haemodynamic response to laryngoscopy or in haemoglobin oxygen saturation before or after tracheal intubation.

Comment

This study has confirmed the faster onset of rocuronium compared with vecuronium and showed that this could be detected clinically, allowing earlier intubation without accurate timing or neuromuscular monitoring. Using clinical judgment alone, intubating conditions were excellent or good in all patients who received rocuronium, although the measured degree of neuromuscular block suggests that the technique was relatively insensitive, and tracheal intubation could probably have been completed earlier, especially as rocuronium may have a faster onset of action at the larynx than at the adductor pollicis.[6] In contrast, clinical signs underestimated the time required for adequate onset of vecuronium.

Clinical judgment is subjective and may vary between individuals. In our study, tracheal intubation was performed by two different anaesthetists (both authors) who used the same technique and attempted to apply the same criteria. Nevertheless, their judgment varied greatly, and one anaesthetist consistently started laryngoscopy and completed tracheal intubation earlier (in both groups) than the other anaesthetist. Both anaesthetists achieved shorter intubation times and lower intubation scores in the rocuronium compared with the vecuronium group. This suggests that while clinical judgment may vary between individuals, the faster onset of rocuronium can be detected consistently.

Despite improved intubating conditions in the rocuronium group, four patients required a bougie to facilitate tracheal intubation. Two of these patients were grade 3 at laryngoscopy, despite being classified as Mallampati class 1 at the preoperative assessment (although more extensive evaluation might have identified potential problems). A bougie was chosen, in preference to alternative manipulations, as it reduced the delay in completing intubation and, in grade 3 patients, lifted the epiglottis sufficiently to see the vocal cords (open in both patients) and complete the Krieg score. The low scores in these patients (5 and 6) suggest that anatomical factors, rather than inadequate relaxation, were responsible for the difficulty.

In summary, clinical judgment adequately predicted satisfactory tracheal intubating conditions after rocuronium, allowing intubation to be completed within an acceptable period of time, although this interval could probably have been shortened by neuromuscular monitoring. In contrast, clinical judgment underestimated the time required for adequate onset of action of vecuronium, resulting in less favourable intubating conditions. Improved intubating conditions had no effect on haemodynamic response or oxygen saturation.

Acknowledgement

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Vecuronium-induced neuromuscular block during xenon or sevoflurane anaesthesia in humans

Y. NAKATA, T. GOTO AND S. MORITA

Summary

Twitch response using accelerometry and plasma concentrations of vecuronium and its metabolite were studied in 27 surgical patients during xenon or sevoflurane anaesthesia after administration of vecuronium 0.05 mg kg^{-1}. Anaesthesia was maintained using oxygen–xenon (MAC=71%) or oxygen–sevoflurane (MAC=2%) at an end-tidal concentration equal to 0.8 MAC (i.e. 57% xenon and 1.6% sevoflurane). Mean time from administration of vecuronium to 25% recovery of the first twitch of the train-of-four response was significantly shorter in the xenon group than in the sevoflurane group (12.9 (SD 2.5) min *vs* 19.4 (6.0) min, respectively). Plasma concentrations of vecuronium at 25% recovery were significantly higher during xenon than during sevoflurane anaesthesia (187 (49) ng ml^{-1} *vs* 136 (40) ng ml^{-1}, respectively), while those of 3-desacetylvecuronium were similar in both groups. (*Br. J. Anaesth.* 1998; **80**: 238–240)

Keywords: anaesthetics gases, xenon; anaesthetics volatile, sevoflurane; monitoring, neuromuscular block; neuromuscular block, vecuronium; neuromuscular block, measurement of response.

Xenon and sevoflurane are inhaled anaesthetics with a low blood-gas solubility coefficient which have been used in conjunction with neuromuscular blocking agents during clinical anaesthesia.[1] Potent inhalation anaesthetics variably influence the neuromuscular blocking effects of neuromuscular blocking agents, and sevoflurane has been evaluated in this respect.[2] However, the neuromuscular blocking effects of xenon have never been evaluated. To characterize the interaction between xenon and non-depolarizing neuromuscular blocking agents, we studied the onset and duration of vecuronium-induced neuromuscular block, and plasma concentrations of vecuronium and 3-desacetylvecuronium under equianaesthetic concentration of xenon and sevoflurane anaesthesia.

Methods and results

After obtaining approval from the Institutional Human Studies Committee of Teikyo University and informed consent, we studied 27 ASA I–II adult patients undergoing elective general, orthopaedic, gynaecological or ENT surgery. No patient had neuromuscular, renal or hepatic disorders or was receiving any medication that might alter neuromuscular transmission. Patients were allocated randomly to one of two groups; 12 patients received xenon and 15 received sevoflurane anaesthesia.[3]

No patient was premedicated. In the operating room, standard monitoring (electrocardiogram, pulse oximetry and non-invasive arterial pressure) was commenced. Arterial pressure was measured at 5-min intervals with a cuff positioned on the right arm. Lactated Ringer's solution was infused slowly via an i.v. cannula inserted in the left antecubital fossa. After induction of anaesthesia with fentanyl 0.5–1.0 μg kg^{-1} and propofol 2–6 mg kg^{-1}, the trachea was intubated without neuromuscular blocking agents. Anaesthesia was maintained with oxygen–xenon (MAC=71%[4]) or oxygen–sevoflurane (MAC =2%) at an end-tidal concentration equal to 0.8 MAC (i.e. 57% xenon and 1.6% sevoflurane). Xenon concentration was monitored continuously at the Y connector with an AZ720 Xenon Monitor (Anzai Medical, Tokyo, Japan) and sevoflurane with an Ultima (Datex, Helsinki, Finland). There is no report in the literature demonstrating intraoperative awareness during anaesthesia with approximately 60% xenon. Even 30% xenon is known to suppress the stress response to noxious stimuli because of its analgesic effects.[5] Thus the concentration of xenon used in this study was expected to provide an adequate level of anaesthesia. A low-flow technique was used for xenon anaesthesia. The lungs were ventilated mechanically to maintain end-tidal carbon dioxide concentration at 4.0–4.7 kPa (Datex Ultima, Helsinki, Finland). Core temperature was maintained at 35.5–37.0°C using warming blankets. The right radial artery was cannulated at the wrist with a 22-gauge cannula and flushed with heparin for blood sampling.

Neuromuscular block was monitored with an accelerometer (TOF-guard; Biometer International, Odense, Denmark). Both arms were extended and the hands were fixed in supination beside the patient with the left thumb allowed to move freely. An accelerometer was attached via silver–silver chloride electrodes over the position of the ulnar nerve at the left wrist. The supramaximal current was determined using the automatic set-up procedure of the TOF-guard. This uses a current of 1 Hz which tests initially the electrode connections at 20 mA and then increases the stimula-

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Table 1 Patient characteristics, doses of propofol and fentanyl administered, times after administration of vecuronium to 90% depression of the first twitch of the train-of-four response (T1/T0) and 25% recovery of T1/T0 (mean (range or SD) or number). Plasma concentrations of vecuronium and 3-desacetylvecuronium are also given. *$P<0.05$ between groups. †$n=12$

	Xenon ($n=12$)	Sevoflurane ($n=15$)
Age (yr)	36.2 (25–47)	39 3 (21–59)
Sex (M/F)	1/11	2/13
Weight (kg)	59 (12)	60 (11)
Propofol (mg kg^{-1})	4.3 (1.2)	4.0 (1.1)
Fentanyl (µg kg^{-1})	2.5 (1.1)	2.5 (0.8)
Time to		
90% depression of T1/T0 (min)	2.7 (0.6)	2.5 (0.7)
25% recovery of T1/T0 (min)*	12.9 (2.5)	19.4 (6.0)
Plasma concentration at 25% recovery of T1/T0		
Vecuronium (ng ml^{-1})*	187 (49)	136 (40)†
3-Desacetylvecuronium (ng ml^{-1})	31 (7)	30 (5)†

tion to 60 mA. Twitch height is adjusted to 100% and the stimulation current is decreased automatically until twitch height starts to decrease. The current corresponding to this decrease is stored and the stimulation current returned to 60 mA. When the supramaximal stimulus had been determined, the stimulator continued to stimulate the ulnar nerve with a train-of-four (TOF) pattern at 15-s intervals. When the response to TOF stimulation was stable, the magnitude of the first twitch of the train was taken as control twitch height. The end-tidal anaesthetic concentration and twitch response were stable for 45 min before administration of vecuronium. All neuromuscular responses were based on the first twitch of the TOF (twitch response).

Approximately 60 min after induction of anaesthesia, vecuronium 0.05 mg kg^{-1} was given i.v. When the twitch response had recovered to 25%, 10 ml of blood were obtained via the arterial cannula for measurement of vecuronium concentration. Onset time was defined as the time from the beginning of administration of vecuronium to 90% depression of the first twitch of the TOF response. Duration of action was defined as the time from the beginning of administration of vecuronium to 25% recovery of the first twitch response. During the study, we monitored clinical signs of potential intraoperative wakefulness, such as lacrimation, sweating and tachycardia. Increases in arterial pressure of more than 20% of baseline were treated immediately with incremental doses of fentanyl 50 µg i.v. On the day after surgery, all the patients were asked if they recalled any perioperative event or felt pain or discomfort during the study.

Blood samples were centrifuged promptly and the plasma removed. Plasma was buffered with NaH_2PO_4, frozen and stored at −35°C for subsequent measurement of concentrations of vecuronium and 3-desacetylvecuronium using gas chromatography [6]. The assay has a sensitivity of 5 ng ml^{-1} and a coefficient of variance of 15% at 10 ng ml^{-1}.

All numerical data were analysed using unpaired *t* tests.[3] $P<0.05$ was considered statistically significant. All values are reported as mean (SD).

There were no significant differences between patient data or doses of propofol and fentanyl in the two groups. All patients achieved at least 90% twitch depression. Duration of action of vecuronium was 25% shorter in the xenon compared with the sevoflurane group (table 1). No patient in either group showed clinical signs of potential intraoperative wakefulness or recalled intraoperative events when interviewed after operation.

We obtained blood samples from 24 patients; we failed to obtain blood samples from three patients in the sevoflurane group because of our inability to cannulate the right radial artery. Plasma vecuronium concentrations were 40% higher during xenon anaesthesia at 25% recovery of the first twitch of the TOF.

Comment

Our findings on the duration of action of vecuronium 0.05 mg kg^{-1} are consistent with previous studies which showed that potent inhalation anaesthetics variably influence non-depolarizing neuromuscular blocking agents,[2] although no direct comparison had been made between xenon and sevoflurane. Our study demonstrated that xenon had a lesser effect on recovery from vecuronium-induced neuromuscular block than sevoflurane.

The similar onset times of vecuronium in the xenon and sevoflurane groups may appear to conflict with their different durations of action. Although the exact mechanism of this similarity was not determined in our study, small doses (0.8 MAC) of inhaled anaesthetics and the small sample sizes could explain the lack of difference in onset time between the two anaesthetic groups.

Plasma concentrations of vecuronium were 40% higher during xenon compared with sevoflurane anaesthesia at similar levels of recovery from block. Assuming that plasma concentrations of vecuronium and 3-desacetylvecuronium reflect those at the neuromuscular junction, this suggests that xenon produces a smaller neuromuscular blocking effect than sevoflurane. However, in our study vecuronium was administered as a bolus, not as a continuous infusion, in order to duplicate our clinical practice. This design did not achieve steady state plasma vecuronium concentrations and may be criticised because of the possible lack of equilibration between the plasma and neuromuscular junction. Therefore, plasma concentrations of vecuronium and 3-desacetylvecuronium in our study may not have reflected concentrations at the neuromuscular junction at that time. We provide only suggestive, but not conclusive, evidence that xenon has lesser pharmacodynamic effects than sevoflurane.

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Current practice of local anaesthesia for routine ocular surgery

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Summary

We surveyed the current practice of local anaesthesia for routine ocular surgery by consultant anaesthetists in the Wessex region using a postal questionnaire. Most consultants were in agreement concerning the type and technique of block, and monitoring to be used during local anaesthesia for ocular surgery. The issue of teaching for trainee anaesthetists produced a varied response. We found that a different level of perioperative preparation and monitoring was used from that recommended by the Joint Working Party on the subject in 1993. (*Br. J. Anaesth.* 1998; **80**: 241–242)

Keywords: anaesthetics local; surgery, ophthalmological; anaesthesia, audit

In March 1993, a Joint Working Party representing the Royal Colleges of Ophthalmology and Anaesthetists published recommendations for the perioperative management of patients undergoing ophthalmic surgery. Using a postal survey, we aimed to observe the extent to which some of these recommendations are now usual practice for consultant anaesthetists in charge of routine ophthalmic lists. We report the views on provision for teaching of local eye blocks to anaesthetic trainees, the type of blocks performed, precautions taken and complications encountered during the time of insertion of the block and in the perioperative period.

Methods and results

Anaesthetic secretaries supplied the names of consultant anaesthetists who regularly attended ophthalmic lists in the Wessex region. A one-page questionnaire, covering letter and self-addressed envelope were sent to 37 consultant anaesthetists. The questionnaire included tick-box responses to questions on who performed local eye blocks, indications for the block and techniques used for the block. We enquired which preoperative investigations were usually performed, if i.v. access was established, and what monitoring was used routinely before the block and in the peroperative period. Details of complications which had been encountered were requested, as were teaching methods available for trainees.

The response rate to the postal survey was 84%. Each consultant attended an average of 1.3 lists per week. The average number of patients per list was 4.4, 61% of whom received local anaesthesia for surgery. Eighteen consultant anaesthetists (61%) gave eye blocks, as did 35% of their trainees. Twenty consultants felt that the most important indication for performing a local block was a serious coexisting medical condition, while four believed that day-case surgery and four that surgical preference were most important. Twenty-three responders performed peribulbar blocks with or without topical anaesthesia. Three consultants performed retrobulbar blocks and five performed both peribulbar and retrobulbar blocks.

Axial length was considered before performing a block by 28 responders (90%) and the position of straight gaze was used by all consultants performing retrobulbar blocks. All consultants used 25-gauge needles. Twelve consultants performing peribulbar blocks used 25-mm, three used 16-mm and one used 38-mm length needles. Two consultants performing retrobulbar blocks used 25-mm and three 38-mm length needles. Two consultants used bupivacaine alone and five used lidocaine with bupivacaine. The remainder used a combination of lidocaine, bupivacaine and hyaluronidase.

Monitoring was instituted before performing a local block by 16 consultants (52%). In the peroperative period, pulse oximetry was used by 31 (97%), ECG by 18 (58%) and indirect arterial pressure monitoring by 10 (32%) consultants. Sixteen consultants (52%) established i.v. access as routine. Twelve of the consultants (39%) requested that patients had the same preoperative investigations as for a general anaesthetic, including full blood count, electrolyte concentrations, ECG and chest x-ray, if appropriate, and all had resuscitation equipment available (table 1).

Nine consultants had encountered retrobulbar haemorrhage as a complication of local eye blocks, one had witnessed respiratory arrest and three had observed the oculocardiac reflex as a result of a block.

Trainees were allowed to perform blocks by 35% of the consultants. Forty-two percent of trainees had been taught by an anaesthetist, 16% had been taught by an ophthalmic surgeon and 10% were taught by both. It was not known who taught the remaining 32% of the trainees performing blocks. Fourteen consultants (45%) felt that there was no need for a specific teaching programme for their juniors; four reported that there was a teaching programme in

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Table 1 Percentage of consultant anaesthetists using preoperative preparation and monitoring, and types of blocks performed

Preoperative preparation	I.v. access and perioperative monitoring	Type of block performed
Monitoring established 52%	I.v. access 52%	Peribulbar 74%
Axial length considered 90%	Pulse oximetry 97%	Retrobulbar 10%
Resuscitation equipment 100%	ECG 58%	Peribulbar or retrobulbar 16%
Prepared as for general anaesthesia 39%	NIAP 32%	25-gauge needle 100%

operation and 10 felt that a programme would be worthwhile.

Comment

The average age of patients on ophthalmic lists in the study by Fisher and Cunningham was 75 yr,[2] of whom 84% suffered from significant systemic illness. Silent myocardial ischaemia in the elderly is well documented, as are side effects relating to multiple drug therapy. It is for these reasons that the Working Party recommended that all patients should be assessed fully before operation. In this study, patients of only 12 consultants (39%) were prepared in the same way as for a general anaesthetic.

Anaesthetists have been implicated in causing a higher rate of complications when performing local anaesthetic blocks than ophthalmic surgeons.[3] Previous reports have indicated that the overall incidence of retrobulbar haemorrhage is approximately 1%. This was the complication most frequently encountered by consultant anaesthetists who performed blocks in this study and by their ophthalmological colleagues who also performed blocks. Unfortunately, we did not establish the frequency with which this or other complications occurred. The consultant who had witnessed respiratory arrest did so once in a series of 2000 patients.

Some studies have disputed that the oculocardiac reflex can be initiated by insertion of a block.[4] In this survey, three consultants reported this reflex occurring while a block was being performed. This may also reflect under-reporting as only 52% of consultants used perioperative monitoring.

The Working Party recommendations state that i.v. access should be mandatory before any anaesthetic intervention but this was standard practice for only 52% of anaesthetists surveyed. The results of this study showed that a different level of perioperative preparation and monitoring was used in practice from that recommended in 1993.[1] The CEPOD report stresses "that practice amongst anaesthetists is not stereotyped but the fact that more than 90% of practitioners do follow certain patterns supports the notion that standards of practice could now be written".[5]

The question must be raised whether peer group practice should be accepted as the standard; the alternative would be to force a change in current practice. A change in practice in dental anaesthesia followed the Poswillo report when the recommendations were based on objective information concerning the risk of arrhythmia. The risks of monitoring are negligible. Surely the institution of ECG monitoring and i.v. access before insertion of the block should remain as a guideline and be accepted as standard practice?

This study showed that despite the absence of formal teaching programmes, most consultants seemed well aware of the potential complications of siting a local eye block, in addition to the current recommendations to reduce the incidence of side effects. The methods of performing blocks and perioperative monitoring of patients were similar throughout the region.

If the practices and opinions of Wessex anaesthetists are representative of national practices, the question arises if recommended guidelines should be changed to fit with current practices. Alternatively, the recommendations could remain and force a change in anaesthetic monitoring for routine ocular surgery.

This survey should be extended nationally. An extended survey questionnaire should be altered to allow recording of the frequency of complications encountered and the opinions of trainee anaesthetists on the best methods and adequacy of training available for regional eye blocks.

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Desflurane maintains intraocular pressure at an equivalent level to isoflurane and propofol during unstressed non-ophthalmic surgery

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Summary

We have investigated the effects of desflurane compared with isoflurane and propofol on intraocular pressure (IOP) in 48 ASA I–II patients undergoing elective non-ophthalmic surgery. Anaesthesia was induced with thiopental 3–5 mg kg^{-1}, fentanyl 2–4 μg kg^{-1} and vecuronium 0.1 mg kg^{-1}. Patients were allocated randomly to receive propofol (n=16) 4–8 mg kg^{-1} h^{-1}, isoflurane (n= 16) or desflurane (n=16) for maintenance of anaesthesia. Fentanyl was added if necessary. The lungs were ventilated with 70% nitrous oxide in oxygen. Arterial pressure, electrocardiography, heart rate and end-tidal carbon dioxide were measured throughout anaesthesia. IOP was measured before surgery, during maintenance and after emergence from anaesthesia with applanation tonometry by an ophthalmologist blinded to the anaesthetic technique. There was a significant decrease in IOP after induction of anaesthesia which did not differ between groups. Desflurane maintained IOP at an equivalent level to isoflurane and propofol. (*Br. J. Anaesth.* 1998; **80**: 243–244)

Keywords: anaesthetics volatile, desflurane; anaesthetics volatile, isoflurane; anaesthetics i.v., propofol; eye, intraocular pressure

One aim of anaesthetic management during ophthalmic surgery is to provide good control of intraocular pressure (IOP). An increase in IOP may be catastrophic in patients with glaucoma or a penetrating open-eye injury. Anaesthesia in these patients must prevent an increase in IOP and provide a "soft" eye which is suitable for surgery and free of haemorrhage, particularly expulsive choroidal haemorrhage.

IOP is determined by the rate of production of aqueous humour and vitreous volume, choroidal blood volume, scleral rigidity, orbicularis oculi muscle tension and external pressure.[1] Many studies have examined the effects of anaesthetics and related drugs on IOP. Inhalation anaesthetics such as halothane and isoflurane decrease IOP by lowering the formation rate of aqueous humour and increasing the trabecular outflow facility.[2 3] The i.v. hypnotic agents propofol and thiopental also decrease IOP and have been demonstrated to attenuate the increase in IOP in response to laryngoscopy and intubation.[4]

Desflurane is a volatile anaesthetic with a low blood-gas solubility coefficient. Recovery from anaesthesia with desflurane is more rapid than with other potent inhalation anaesthetic agents and comparable with propofol. Because of its irritant properties on the airway, desflurane is not suitable for inhalation induction of anaesthesia in ophthalmic patients, but it may be an ideal maintenance anaesthetic. In dogs, desflurane (7.0% expired) was associated with a baseline IOP of 11.3 (SD 3.8) mm Hg[5]: normal IOP is approximately 15 mm Hg, with a "normal" range of approximately 10–20 mm Hg.

There have been no studies on the effects of desflurane on IOP in humans. We performed a randomized, prospective, single-blind study to compare the effects of desflurane, isoflurane and propofol on IOP in patients undergoing elective non-ophthalmic surgery.

Methods and results

After obtaining approval from the Ethics Committee of Vienna General Hospital, we studied 48 patients undergoing elective non-ophthalmic surgery. Inclusion criteria were age 16–60 yr, ASA I or II, no known allergies or adverse reactions to any of the anaesthetic agents used in the study, and no pre-existing ophthalmic disease. Before surgery, patients were allocated randomly to one of three groups: propofol (n=16), isoflurane (n=16) or desflurane (n=16). All patients were premedicated with midazolam 7.5 mg, 1 h before surgery. Anaesthesia was induced with fentanyl 2–4 μg kg^{-1}, thiopental 3–5 mg kg^{-1} and vecuronium 0.1 mg kg^{-1}. Ventilation was adjusted to maintain end-tidal carbon dioxide partial pressure at 4.3–4.6 kPa. Anaesthesia was maintained with continuous infusion of propofol 4–8 mg kg^{-1} h^{-1} (n=16) or 1 MAC of isoflurane or desflurane. The lungs were ventilated with 70% nitrous oxide in oxygen. Arterial pressure, electrocardiography, heart rate, oxygen saturation, end-tidal carbon dioxide concentration and nasopharyngeal temperature were measured throughout anaesthesia. IOP was obtained by a hand-held applanation tonometer (Perkins). Patients were positioned supine for examination. All measurements were made by one ophthalmologist blinded to the

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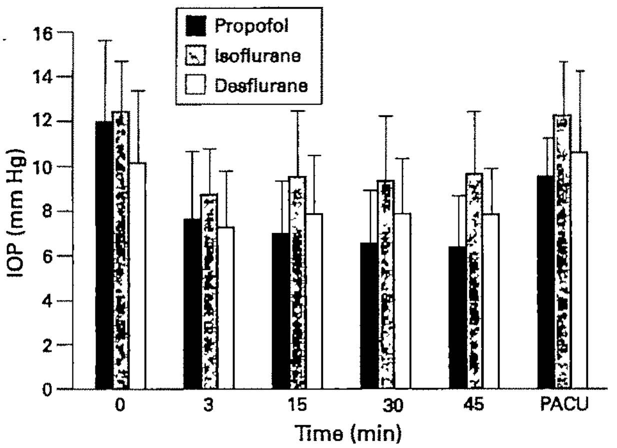

Figure 1 Mean (SD) intraocular pressure (IOP) in the propofol, isoflurane and desflurane groups. PACU=Post-anaesthesia care unit.

anaesthetic technique. IOP was measured before induction of anaesthesia, immediately before intubation, 1, 3, 5 and 10 min after intubation, every 15 min during anaesthesia and at least 1 min after extubation. A final measurement was performed in the recovery room.

One-way ANOVA with Scheffé's *post hoc* test was used to compare baseline data. ANOVA for repeated measures and paired *t* tests were used to assess differences within groups. Correlations were performed using Pearson's correlation coefficient. All data are presented as mean (SD). $P<0.05$ was considered significant.

All patients were evaluated and were comparable in age, weight, sex and duration of operation. Baseline values of mean arterial pressure (MAP), heart rate and IOP were similar between groups. After induction of anaesthesia, IOP decreased significantly 1 min after the end of induction (propofol group, $P<0.05$; isoflurane and desflurane groups, $P<0.01$). During maintenance of anaesthesia, there were no significant changes in IOP over time in any group (fig. 1). In the recovery room, IOP returned to baseline in the desflurane and isoflurane groups, but remained significantly lower in the propofol group ($P<0.01$). MAP and heart rate decreased significantly from baseline (both $P<0.01$) during anaesthesia but increased towards baseline in the recovery room. There were no significant differences in MAP or heart rate between groups. No correlation was found between MAP, heart rate and IOP values.

Comment

The results of this study demonstrated that induction of anaesthesia significantly decreased IOP. Maintenance of anaesthesia with desflurane sustained a low IOP at a level equivalent to that of isoflurane and propofol.

Many factors (in addition to glaucoma) influence IOP, such as genetic status, age, refractive error and race. In addition, IOP is dependent on PEEP ventilation, $P\mathrm{A}'_{\mathrm{O_2}}$ and $P\mathrm{A}'_{\mathrm{CO_2}}$. Any acute increase in intra-abdominal or intrathoracic pressure, not infrequently observed during extubation, may increase IOP. Particular attention must be paid to induction of and emergence from anaesthesia as both mechanical and pharmacological stresses have an amplifying effect on IOP. Most anaesthetic and hypnotic agents, including volatile anaesthetics, barbiturates, opioids, neuroleptics and benzodiazepines decrease IOP in proportion to the depth of anaesthesia. Jantzen emphasized the importance of anaesthetic drugs for general anaesthesia in ophthalmic surgery.[6] He reported that i.v. anaesthetics and volatile agents reduce IOP, with the possible exception of ketamine.

There have been no studies assessing the influence of desflurane on IOP in humans. Artru demonstrated the influence of desflurane and halothane anaesthesia on IOP in dogs.[5] Both halothane and desflurane decreased IOP by approximately 7 mm Hg from baseline values in unanaesthetized dogs, with no difference between groups.

The results of our study indicate that desflurane, in common with isoflurane and propofol, maintained low IOP values during anaesthesia in patients undergoing non-ophthalmic surgery. The decrease in IOP after induction of anaesthesia was sustained if maintenance was provided by desflurane, isoflurane or propofol. In all groups, IOP increased towards baseline values after emergence from anaesthesia. Interestingly, IOP values remained significantly lower compared with baseline in the propofol group. We conclude that desflurane was as safe as isoflurane and propofol for maintenance of anaesthesia. The sustained low IOP after propofol anaesthesia may be beneficial in patients at risk and remains to be evaluated.

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Intraperitoneal bupivacaine or lidocaine does not provide analgesia after total abdominal hysterectomy

P. B. ALI, B. R. COTTON, K. M. WILLIAMSON AND G. SMITH

Summary

We have compared pain scores at rest and on standardized movement, and morphine consumption using patient-controlled analgesia in 60 patients who had undergone total abdominal hysterectomy. Patients were allocated randomly to one of three groups: in the saline group, 0.9% sodium chloride 50 ml was administered into the pelvic cavity before closure of the peritoneum; in the second group, the solution administered was 20 ml of 0.5% bupivacaine solution with epinephrine 1:200 000 diluted with saline to a final volume of 50 ml; in the third group, the solution used was 20 mg of 2% lidocaine with epinephrine 1:200 000 diluted with saline to a final volume of 50 ml. We found that there was no significant difference between the three groups in visual analogue pain scores at 8, 12, 36 or 48 h after operation at rest or on movement, and no significant difference in sedation or dose of antiemetic administered. Mean morphine consumption in the first 24 h was 54.6 (SEM 5.9) mg in the saline group, 55.5 (6.4) mg in the bupivacaine group and 52.5 (5.3) mg in the lidocaine group. In the second 24 h, morphine consumption was 34.9 (6.6) mg, 28.1 (3.5) mg and 28.0 (3.5) mg in the three groups, respectively. We conclude that i.p. administration of local anaesthetic solution into the pelvic cavity did not confer appreciable analgesia in patients undergoing abdominal hysterectomy. (*Br. J. Anaesth.* 1998; **80**: 245–247)

Keywords: anaesthetics local, lidocaine; anaesthetics local, bupivacaine; analgesia, postoperative; surgery, gynaecological

Recently, we conducted a preliminary study[1] comparing saline with a relatively modest dose of lidocaine (200 mg) administered into the peritoneal cavity after total abdominal hysterectomy to determine if the resultant plasma concentrations of local anaesthetic were within a safe range and whether or not there was any appreciable analgesic effect. We found that there was a small but statistically significant difference in pain scores at rest between the saline and lidocaine groups but no significant difference in morphine consumption by patient-controlled analgesia (PCA) or pain scores during movement; plasma concentrations of lidocaine were below the toxic range. That study also provided pilot data on which to base a power analysis for this study, which was designed to see if a larger dose of lidocaine or a longer acting local anaesthetic (bupivacaine) produced analgesia in this situation.

Methods and results

After obtaining approval from the Leicestershire Ethics Committee and written informed consent, we studied 60 patients undergoing total abdominal hysterectomy. All patients were aged 20–60 yr, ASA I or II, not undergoing surgery for malignancy, and were scheduled for surgery undertaken via a standard Pfannenstiel incision. Patients were excluded if they had hepatic, vascular or cardiac disease, or allergy to local anaesthetic agents.

The anaesthetic technique was standardized and comprised premedication with temazepam 10 mg, 1–2 h before operation. Anaesthesia was induced with a sleep dose of propofol 150–200 mg, followed by vecuronium 0.1 mg kg^{-1}. After tracheal intubation the lungs were ventilated artificially with a mixture of 1.5–2% enflurane and 66% nitrous oxide in oxygen. Shortly after induction of anaesthesia, morphine 10 mg was administered as a standard bolus to all patients, together with prochlorperazine 12.5 mg.

After removal of the uterus, the anaesthetist opened a sealed envelope indicating to which group the patient was allocated; each patient's number was drawn from a list of computer-generated random numbers. In the saline group, the anaesthetist prepared a syringe containing 50 ml of sterile 0.9% sodium chloride, in the bupivacaine group 50 ml of 0.2% bupivacaine with epinephrine (1:500 000 dilution, prepared by adding 30 ml of saline to 20 ml of 0.5% bupivacaine containing epinephrine 1:200 000) and in the lidocaine group 50 ml of 0.8% lidocaine with epinephrine (1:500 000 dilution, prepared by adding 30 ml of saline to 20 ml of 2% lidocaine containing epinephrine 1:200 000). One of these three solutions was administered into the pelvic cavity before closure of the peritoneum and anterior abdominal wall. The hysterectomy was carried out using a standard technique; the peritoneum over the vault of the vagina was not closed and the solution was instilled into the pelvic cavity after haemostasis

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Table 1 Patient characteristics, and pain and sedation scores in the three groups (mean (SEM or range))

	Saline (n=20)	Bupivacaine (n=20)	Lidocaine (n=20)
Age (yr)	41.3 (30–59)	41.6 (29–59)	40.9 (28–58)
Weight (kg)	67.6 (2.9)	62.4 (2.2)	64.5 (1.9)
PCA morphine consumption (mg)			
0–24 h	54.6 (5.9)	55.5 (6.4)	52.5 (5.3)
24–48 h	34.9 (6.6)	28.1 (3.5)	28.0 (3.5)
Pain scores at rest (mm)			
8 h	36 (5.3)	35 (5.4)	26 (4.0)
12 h	27 (5.5)	23 (6.3)	26 (5.1)
24 h	25 (4.7)	30 (5.6)	19 (3.3)
36 h	15 (3.2)	17 (4.3)	14 (3.1)
48 h	14 (5.4)	14 (3.2)	11 (3.4)
Pain scores on movement (mm)			
8 h	48 (6.7)	50 (5.6)	36 (5.8)
12 h	42 (7.2)	35 (8.9)	36 (6.6)
24 h	50 (6.3)	41 (6.1)	45 (3.6)
36 h	29 (5.1)	25 (5.4)	27 (5.6)
48 h	28 (6.7)	25 (3.7)	26 (4.6)
Sedation (mm)			
8 h	28 (6.6)	38 (6.9)	41 (7.7)
12 h	43 (8.4)	59 (8.3)	52 (8.6)
Dose of prochlorperazine in the first 24 h (mg)	12.5 (0.0)	12.5 (0.0)	13.1 (0.6)

had been secured, when all packs had been removed from the peritoneal cavity and the patient was placed in the supine horizontal position.

The patients, surgeons, theatre nursing staff, pain sister responsible for conducting observations in the postoperative period and the ward nursing staff were unaware of the groups to which patients were allocated.

In the recovery room, patients were provided with patient-controlled analgesia equipment (Abbott PCA II); this was programmed to deliver morphine in 1-mg boluses with a 5-min lockout period, the use of which had been explained to the patient at the preoperative interview. In our unit, it is policy to allow the pain sister to administer bolus doses of morphine up to 5 mg i.v. in the recovery unit in order to provide optimum analgesia before the patient commences self-administration of morphine; if 5 mg is inadequate, the anaesthetist is called to provide optimum analgesia before the patient is returned to the ward.

In the postoperative period, pain scores were recorded by the patient using a linear analogue score (10-cm scale: 0=no pain, 100=maximum pain conceivable) at 8, 12, 24, 36 and 48 h at rest and on movement, which was standardized as elevation from the horizontal to the supine position. Sedation scores were also recorded at 8- and 12-h intervals using a linear analogue score (0=wide awake, 100=drowsy to the point of sleeping).

From a power analysis conducted on our preliminary study, we calculated that this study had a 90% power to detect a two-sided significant difference at the 5% level of 20 mm in pain scores, 20 mg in morphine consumption in the first 24 h and a 31-mg difference in morphine consumption in 48 h.

Data were analysed using SPSS on an IBM-compatible PC. Data were initially subjected to a Komolgorov–Smirnov goodness-of-fit test and if found to be distributed normally, were then analysed using MANOVA with Scheffé and Bonferroni *post hoc* tests. Non-normally distributed data were analysed by Kruskal–Wallis tests.

The three groups were comparable in age and weight, and there were no significant differences in any variable between the three groups. In particular, there was no significant difference in morphine consumption in the first or second 24 h after operation and no significant difference in pain scores at rest or during movement (table 1). The dose of morphine given in each group in the first 24 h includes any bolus given in the recovery room but not during anaesthesia. Approximately 20% of all patients were given a bolus dose in the recovery room and there was no difference between groups in the numbers of patients receiving these boluses.

Comment

Recently, there has been interest in the use of peritoneal administration of local anaesthetic as a means of controlling pain after surgery. For laparoscopic sterilization, local anaesthetic may be injected into the mesentery of the fallopian tube, but in 1991 Narchi, Benhamou and Fernandez described the use of large volumes of dilute local anaesthetic administered into the peritoneal cavity for treatment of pain after laparoscopy. Using the standard maximum recommended doses of both lidocaine and bupivacaine with epinephrine, these workers demonstrated significant reductions in mean pain scores in the local anaesthetic groups from 8 to 24 h after surgery compared with a control group in which saline was administered into the intraperitoneal cavity.[2 3] A subsequent study revealed that plasma concentrations of lidocaine and bupivacaine after i.p. instillation of quite large doses of local anaesthetic did not approach toxic plasma concentrations.[4] Subsequently, it was shown that after laparoscopic cholecystectomy, pain was reduced after administration of 20 ml of 0.25% bupivacaine into the region of the gall bladder during surgery; although plasma concentrations of local anaesthetic were not measured, no patient exhibited clinical signs of toxicity.[5]

Recently, we undertook a preliminary study on i.p. installation of local anaesthetic after total abdominal hysterectomy, partly to determine the rate of absorption of lidocaine from the peritoneal cavity and partly to provide the basis of a power analysis for conducting this study.[1] In that preliminary study, we found that plasma concentrations of lidocaine after an i.p. dose of 200 mg did not approach toxic concentrations, thus reassuring us that it was reasonable to undertake the present study using lidocaine 400 mg.

We found that there was no significant difference in pain scores or morphine consumption for 48 h after operation in patients given lidocaine 400 mg, bupivacaine 100 mg or saline into the peritoneal cavity after total abdominal hysterectomy. This suggests that the difference in pain scores at rest found in our preliminary study was probably a chance observation. Indeed, that finding of a 13-mm difference in pain scores at rest at 24 h and 11 mm at 48 h was not accompanied by any difference in pain scores on movement. There was also no difference in morphine consumption between the lidocaine and saline groups.

The few studies on the use of i.p. administration of local anaesthetic in minor gynaecological surgery (laparoscopy) seem to have found consistently that the technique produced analgesia.[2,3,5] However, with major intra-abdominal surgery, the results are conflicting. Only two groups have claimed benefit for i.p. local anaesthetic after laparoscopic cholecystectomy[5,6] but a more substantial study by Joris and co-workers[7] failed to obtain any effect of i.p. bupivacaine on pain after laparoscopic cholecystectomy, despite the fact that visceral pain was demonstrated to account for most of the pain after this procedure. On the basis of both the present and our previous preliminary study, we also conclude that i.p. administration of local anaesthesia fails to confer appreciable analgesia in patients undergoing major gynaecological abdominal surgery.

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Prevention of postoperative nausea and vomiting in female patients during menstruation: comparison of droperidol, metoclopramide and granisetron

Y. FUJII, H. TOYOOKA AND H. TANAKA

Summary

The incidence of postoperative nausea and vomiting (PONV) is high in women during menstruation. We have compared the efficacy of droperidol, metoclopramide and granisetron in the prevention of PONV in female patients during menstruation undergoing major gynaecological surgery. In a randomized, double-blind study, 120 patients received droperidol 25 µg kg^{-1}, metoclopramide 0.2 mg kg^{-1} or granisetron 40 µg kg^{-1} (*n*=40 in each group) i.v. immediately before induction of anaesthesia. A standard general anaesthetic technique and postoperative analgesia were used throughout. There was a complete response, defined as no PONV and no administration of rescue medication, during the 24-h observation period in 45% of patients in the droperidol group, 38% in the metoclopramide group and 70% in the granisetron group (P= 0.021 *vs* droperidol, P=0.003 *vs* metoclopramide). There was no difference in the incidence of adverse events between groups. We conclude that the prophylactic antiemetic efficacy of granisetron was superior to that of droperidol or metoclopramide for prevention of PONV in women during menstruation. (*Br. J. Anaesth.* 1998; **80**: 248–249)

Keywords: vomiting, nausea; vomiting, nausea, patient factors; vomiting, antiemetics, droperidol; vomiting, antiemetics, metoclopramide; vomiting, antiemetics, granisetron

Postoperative nausea and vomiting (PONV) are common and distressing symptoms in women after major gynaecological surgery performed under general anaesthesia. The aetiology of PONV after gynaecological surgery is multifactorial and includes age, obesity, history of motion sickness, previous postoperative emesis, type of surgery, anaesthetic technique and postoperative pain.[1] It has been reported that the incidence of PONV varies according to the phase of the menstrual cycle and a high incidence is associated with menstruation.[2] We have recently demonstrated that granisetron, a selective 5-hydroxytryptamine type-3 (5-HT$_3$) receptor antagonist, reduces the incidence of PONV in female patients during menstruation.[3] This study was designed to compare the efficacy of droperidol, metoclopramide and granisetron in the prevention of PONV in women during menstruation after major gynaecological surgery.

Methods and results

After obtaining approval from the Institutional Review Board and informed consent, we studied 120 ASA I or II women, aged 21–46 yr, during menstruation. The latter was elicited during routine enquiring. Patients who had gastrointestinal diseases and those who had received an antiemetic within 24 h before surgery were excluded.

Patients were allocated randomly to receive one of three treatment regimens: droperidol 25 µg kg^{-1}, metoclopramide 0.2 mg kg^{-1} or granisetron 40 µg kg^{-1} administered i.v. immediately before induction of anaesthesia.

Patients received no premedication. An extradural catheter was inserted at the L2–3 or L3–4 interspace and advanced into the extradural space. Anaesthesia was induced with thiopental 5 mg kg^{-1} i.v., and vecuronium 0.2 mg kg^{-1} i.v. was used to facilitate tracheal intubation. Anaesthesia was maintained with 1.0–3.0% (inspired concentration) isoflurane and 66% nitrous oxide in oxygen. Ventilation was controlled mechanically and adjusted to maintain PE'_{CO_2} at 4.6–5.2 kPa. A nasogastric tube was inserted and suction applied to empty the stomach of air and other contents. When haemodynamic variables were stable, 1.5% lidocaine 10–15 ml were injected via the extradural catheter. Neuromuscular block was produced with vecuronium as required. At cessation of surgery, atropine 0.02 mg kg^{-1} i.v. and neostigmine 0.04 mg kg^{-1} i.v. were administered for antagonism of neuromuscular block, and the trachea was extubated. After tracheal extubation, the nasogastric tube was suctioned and removed. If two or more episodes of vomiting occurred during the first 24 h after anaesthesia, another rescue antiemetic was given. Postoperative analgesia was provided with a mixture of 0.25% bupivacaine 40 ml and morphine 0.1 mg kg^{-1}. Patients in all groups were also allowed to receive indomethacin for intolerable pain.

Complete response, defined as no PONV (nausea, retching and vomiting) and no rescue antiemetic

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Table 1 Patient characteristics and incidence of complete response (no PONV, no rescue) (mean (SD or range) or number (%). P_1 values=droperidol *vs* metcolopramide; P_2 values=droperidol *vs* granisetron; P_3 values=metoclopramide *vs* granisetron

	Droperidol (*n*=40)	Metoclopramide (*n*=40)	Granisetron (*n*=40)	P_1	P_2	P_3
Age (yr)	38 (25–46)	38 (21–46)	38 (23–45)	ns	ns	ns
Height (cm)	155 (5)	156 (5)	155 (4)	ns	ns	ns
Weight (kg)	53 (7)	54 (6)	55 (7)	ns	ns	ns
History of motion sickness (*n*)	4	4	4	ns	ns	ns
History of previous PONV (*n*)	2	2	2	ns	ns	ns
Duration of operation (min)	83 (35)	81 (32)	83 (34)	ns	ns	ns
Duration of anaesthesia (min)	105 (35)	104 (33)	110 (33)	ns	ns	ns
Postoperative analgesia						
Morphine (mg, extradural)	5.3 (0.7)	5.4 (0.6)	5.5 (0 8)	ns	ns	ns
Indomethacin (mg)	6.3 (16.7)	7 5 (18.1)	6.3 (16.7)	ns	ns	ns
Types of operation (*n*)						
Abdominal hysterectomy	32	32	33	ns	ns	ns
Vaginal hysterectomy	3	2	2	ns	ns	ns
Salpingo-oophorectomy	5	6	5	ns	ns	ns
Complete response (no PONV, no rescue)	18 (45%)	15 (38%)	28 (70%)	0.325	0.021	0.003
Nausea	11 (28%)	12 (30%)	5 (13%)	0.5	0.081	0.049
Retching	2 (5%)	2 (5%)	1 (3%)	0.179	0.5	0.5
Vomiting	9 (23%)	11 (28%)	6 (15%)	0.398	0 284	0.137
Rescue	6 (15%)	7 (18%)	0 (0%)	0.5	0.013	0 006

medication during the first 24 h after anaesthesia, was recorded by nursing staff without knowledge of which antiemetic the patient had received.

Statistical analyses of the data between groups were performed by ANOVA with Bonferroni correction for multiple comparison, chi-square test or Fisher's exact exact probability test, where appropriate. $P<0.05$ was considered significant. All values are expressed as mean (SD) or number (%). We set $\alpha=0.05$ and $\beta=0.8$, and used a large magnitude of effect (effect size 0.8) to estimate a sufficient sample size. The analysis showed that 40 patients per treatment group would be sufficient.

Patient characteristics and surgical procedures did not differ between groups. During the 24-h observation period, the incidence of complete response (no PONV, no rescue) was 45% in the droperidol group, 38% in the metoclopramide group and 70% in the granisetron group (P=0.021 *vs* droperidol; P= 0.003 *vs* metoclopramide). Six patients who had received droperidol and seven who had received metoclopramide received a rescue antiemetic, compared with none who had received granisetron ($P<0.05$) (table 1). There were no adverse effects in any group.

Comment

In previous studies the incidence of PONV in female patients undergoing gynaecologic laparoscopic surgery increased during the first 8 days of their menstrual cycle (menstruation). We also demonstrated that the incidence of PONV in patients receiving placebo during menstruation was higher than that during non-menstruation.[3] The precise mechanism of an apparent increase in the incidence of PONV during the menstrual period is not known. However, it has been postulated that changing concentrations of follicle-stimulating hormone (FSH) or oestrogen, or both, may sensitize the chemoreceptive trigger zone or the vomiting centre, or both.[2] Several factors, including age, sex, obesity, history of motion sickness or previous PONV, operative procedure, anaesthetic technique and postoperative pain are also considered to increase the incidence of PONV after general anaesthesia for elective surgery.[1] In this study, however, the groups were similar in patient characteristics, surgical procedures, anaesthetic administered and analgesics used after operation. Therefore, the difference in the incidence of PONV between the groups was attributable to the differences in the agents administered.

Granisetron has already been shown to be an effective treatment for cisplatin-induced nausea and vomiting.[4] We have demonstrated that granisetron 40 μg kg^{-1} was effective in preventing PONV after gynaecological surgery,[5] and have recently demonstrated that it reduces the incidence of PONV regardless of the menstrual cycle.[2] This study also demonstrated that the incidence of complete response (no PONV, no rescue) in female patients during menstruation who had received granisetron was remarkably high and significantly better than droperidol 25 μg kg^{-1} or metoclopramide 0.2 mg kg^{-1}.

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Effects of isoflurane–nitrous oxide anaesthesia on insulin secretion in female patients

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Summary

In vitro studies suggest that volatile anaesthetic agents may directly inhibit insulin secretion. It is unclear if supplementation of anaesthesia with isoflurane impairs insulin secretion. We performed a 5-g i.v. glucose tolerance test in 21 patients before and during anaesthesia which was maintained with either 1 or 2 MAC of isoflurane in nitrous oxide, or no volatile agent. The study was carried out before surgery to avoid the influence of hormonal responses to trauma. A significant glycaemic response occurred during both i.v. glucose tolerance tests in all three groups of patients. Serum insulin concentrations were measured and the acute increase in insulin concentration at 3 min and area under the curve for 15 min were calculated. Both variables decreased significantly in all three groups during the tests performed under anaesthesia compared with tests carried out before anaesthesia. (*Br. J. Anaesth.* 1998; **80**: 250–252)

Keywords: hormones, insulin; sympathetic nervous system, catecholamines; metabolism, glucose; metabolism, insulin; anaesthetics volatile, isoflurane

Surgical trauma results in a hormonal and metabolic response, which includes an increase in the concentrations of catabolic hormones and hyperglycaemia. *In vitro* experiments showed a significant inhibitory effect of volatile anaesthetic agents on insulin secretion from rat pancreatic islets.[1 2] Direct impairment of insulin release in humans by these agents may augment the glycaemic response to catabolic hormone secretion found in the perioperative period.

There are few clinical studies on the effects of inhalation anaesthesia on insulin secretion. Therefore, we have studied the insulin response to a 5-g i.v. glucose tolerance test (ivgtt) in healthy patients, both awake and during anaesthesia with 1 or 2 MAC of isoflurane in nitrous oxide, or an anaesthetic without a volatile agent, to determine if there was a specific inhibitory effect of isoflurane on insulin secretion.

Methods and results

The study was approved by the local Hospital Research Ethics Committee. Patients were undergoing elective tubal surgery for infertility. Any subject known to have polycystic ovarian disease, or metabolic or endocrine disorder, or receiving drugs known to alter hormone secretion and metabolism was excluded. All patients gave written, informed consent to the study.

Patients fasted overnight and the studies started in the morning. Premedication with morphine 10 mg and hyoscine 0.4 mg i.m. was given immediately before transfer from the ward.

Two control blood samples were obtained from a central venous catheter and, after 5 min, 50% glucose 10 ml was given i.v. as a bolus into the contralateral arm. Blood samples were obtained after 3, 4, 5, 7, 10 and 15 min. At the end of the awake ivgtt, after the 15-min sample, the patient rested until 60 min.

On completion of the first ivgtt, sealed envelopes were used to allocate patients randomly to receive 0, 1 or 2 MAC of isoflurane in 70% nitrous oxide after induction of anaesthesia. Fentanyl 2 μg kg^{-1} i.v. was given and anaesthesia was induced with thiopental. The trachea was intubated after vecuronium 0.1 mg kg^{-1} and the lungs were ventilated with 70% nitrous oxide in oxygen and isoflurane, as determined by study allocation. Continuous monitoring of partial pressure of expired carbon dioxide and of inspired and expired isoflurane was undertaken and expired carbon dioxide maintained at 4.5–5.0 kPa. In those patients allocated to receive 1 or 2 MAC of isoflurane, the designated partial pressure was achieved rapidly by adjusting the inspired isoflurane concentration (5–10 min after intubation).

Blood samples were collected immediately after induction of anaesthesia and intubation, and 10 min after steady end-tidal isoflurane values at the required MAC were achieved. A similar interval was allowed in patients allocated to the 0 MAC group before collection of another sample. The ivgtt was then repeated during anaesthesia and blood samples collected after 3, 4, 5, 7, 10 and 15 min. Supplements were made to the anaesthetic, where appropriate, and surgery started.

Samples were analysed for blood glucose, serum insulin and cortisol, and plasma catecholamines concentrations, as described previously.[3] For each patient, the insulin response to each ivgtt was calculated as the area under the curve (AUC) from 0 min to the 15 min sample by the trapezium method. The acute insulin response (AIR) was calculated as the absolute increase in insulin concentration from the

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Table 1 Acute insulin response (AIR) and insulin response (AUC) 0–15 min, in each patient. Between-group differences in AIR: awake P =0.54, anaesthetized P=0.26. Between-group differences in AUC: awake P=0.31, anaesthetized P=0.05

	0 MAC		1 MAC		2 MAC	
Patient No.	Awake	Anaes	Awake	Anaes.	Awake	Anaes.
Acute insulin response (AIR) (mu litre^{-1})						
1	57.0	35.0	27.4	13.0	45.2	31.9
2	110.9	54.7	42.3	5.9	27.7	16.1
3	44.4	53.5	46.9	39.2	20.3	14.9
4	18.0	22.5	42.9	27 5	25.7	11.8
5	38.0	11.7	7.8	3.3	65.7	65 4
6	84.5	33.3	24.0	32 5	86.6	90 1
7	28.5	16.9	45.6	10.8	22.5	18 0
Median (range)	44.4	33.3	42.3	13.0	27.7	18.0
	(18.0–110.9)	(11.7–54.7)	(7.8–46.9)	(3.3–39.2)	(20.3–86.6)	(11.8–90.1)
Within-group comparison	P<0.05		P<0.05		P<0.05	
Insulin response (AUC) 0–15 min (mu litre^{-1} min^{-1})						
1	488	219	148	52	225	134
2	722	465	225	108	189	72
3	564	290	234	183	198	58
4	78	119	304	151	221	88
5	251	191	215	28	346	210
6	412	270	133	161	448	413
7	169	139	239	117	153	96
Median (range)	412 (78–564)	219 (119–465)	225 (148–304)	117 (28–183)	221 (189–448)	96 (58–413)
Within-group comparison	P<0.05		P<0.05		P<0.02	

baseline sample immediately preceding each ivgtt to the value of the 3-min sample.[4]

Differences in blood glucose values within each group with respect to the baseline sample of each ivgtt were analysed by two-way analysis of variance with Dunnet's test. Differences between the three groups were estimated by one-way analysis of variance. For insulin data, statistical analysis of differences in the calculated AIR and AUC between the three groups, awake and asleep, was by the Kruskal–Wallis test. Within each group, differences between the two ivgtts were analysed by Wilcoxon matched pairs signed rank sum test. P<0.05 was taken to be statistically significant.

We studied 27 patients. At operation, six patients were found to have ovaries with a polycystic appearance and were excluded from analysis. The results from seven patients were evaluated in each group. Median age was 31 (range 26–36), 32 (29–38) and 29 (24–39) yr for the 0, 1 and 2 MAC groups, respectively. Mean weight was 62.2 (SD 3.2), 59.4 (5.9) and 56.7 (7.4) kg, respectively, for the 0, 1 and 2 MAC groups. No patients reported any event which suggested awareness during the study.

In the awake ivgtt, blood glucose increased significantly in all three groups at 3 min by at least 2.6 mmol litre^{-1} (P<0.05). There was no significant difference in glucose values between the three groups of patients. A similar glycaemic response was seen in the ivgtt during anaesthesia, but the increase was significantly greater in the 2 MAC group at 3 min (F= 7.34, P=0.008). At 15 min, blood glucose concentration was greater in the 1 and 2 MAC groups than in the 0 MAC group (F=6.57, P=0.012).

Both AIR and AUC decreased significantly in all three groups during anaesthesia. However, there was no difference between the groups, either awake or anaesthetized, in AIR or AUC (table 1).

There were no significant differences in circulating norepinephrine, epinephrine or cortisol concentrations between the three groups.

Mean arterial pressure (MAP) did not change significantly in any group during the awake ivgtt. It decreased in all groups after induction of anaesthesia, although this was significant only in the 1 and 2 MAC groups (P < 0.05). Changes in heart rate during the study mirrored those of MAP.

Comment

We have found that after induction of anaesthesia, the insulin response to a 5-g ivgtt decreased significantly compared with the same test performed awake. The only relevant previous clinical study of isoflurane used a large dose of glucose (0.33 mg kg^{-1} i.v.) that resulted in circulating glucose values of up to 20 mmol litre^{-1}.[5] More importantly, the investigators did not examine the effects of anaesthesia without volatile supplementation.

The influence on insulin secretion of the other drugs used in this study (morphine, hyoscine, fentanyl, thiopental and nitrous oxide) cannot be excluded. However, these agents were common to all three groups and indicate that short-term exposure to isoflurane in a clinical setting does not further decrease insulin release. A group size of nine was chosen for the clinical studies as this sample size was adequate to decrease insulin secretion two-fold *in vitro*. However, six patients were excluded, and therefore the power of the study was reduced to 45% with a standardized difference of 1.0.

Cardiovascular depression after induction of anaesthesia may lead to a decrease in splanchnic blood flow with a consequent decrease in insulin reaching the peripheral circulation. Isoflurane anaesthesia results in vasodilatation of the splanchnic bed in humans and an increase in blood flow. In dogs, mechanical reduction of pancreatic blood flow was not associated with a proportionate decrease in insulin release.[6] Thus isoflurane is unlikely to have a major inhibitory effect on insulin release mediated by alterations in splanchnic blood flow.

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Relationship between end-tidal and arterial carbon dioxide partial pressure using a cuffed oropharyngeal airway and a tracheal tube

Y. NAKATA, T. GOTO, S. UEZONO, F. SASAKI AND S. MORITA

Summary

We have compared the differences between end-tidal $P\text{E}'_{\text{CO}_2}$ and arterial Pa_{CO_2} carbon dioxide partial pressures during general anaesthesia using either a cuffed oropharyngeal airway (COPA) or a tracheal tube (TT) in spontaneously breathing adult patients. After induction of anaesthesia, a COPA was inserted in 20 patients who were allowed to breathe spontaneously. When steady state was reached, $P\text{E}'_{\text{CO}_2}$ and Pa_{CO_2} were recorded. The COPA was removed, the trachea intubated with a TT and spontaneous ventilation allowed to resume. After a stable $P\text{E}'_{\text{CO}_2}$ was re-established, Pa_{CO_2} was measured again and $P\text{E}'_{\text{CO}_2}$ recorded. Mean difference between Pa_{CO_2} and $P\text{E}'_{\text{CO}_2}$ with the COPA was 0.72 (SD 0.45) kPa and with the TT 0.64 (0.40) kPa (ns; paired *t* test). Our results suggest that $P\text{E}'_{\text{CO}_2}$ is a clinically acceptable indicator of Pa_{CO_2} in adults breathing spontaneously via a COPA. (*Br. J. Anaesth.* 1998; **80**: 253–254)

Keywords: anaesthesia, general; equipment, tubes tracheal; equipment, cuffs oropharyngeal; monitoring, carbon dioxide; carbon dioxide, partial pressure; partial pressure, carbon dioxide

The cuffed oropharyngeal airway (COPA) is a new airway device which is being introduced into clinical practice. It is an oral airway with a cuff to seal the pharynx and lift the tongue. It can also be connected directly to the anaesthesia breathing system. It is similar to the laryngeal mask airway (LMA) in that it is designed predominantly for use in spontaneously breathing patients and enables anaesthetists to avoid tracheal intubation. The advantages of the COPA compared with the LMA may be that placement is easier to learn, less traumatic and less stimulating.

When the trachea is intubated with a tracheal tube (TT), end-tidal carbon dioxide partial pressure ($P\text{E}'_{\text{CO}_2}$) is used widely as an indicator of arterial carbon dioxide partial pressure Pa_{CO_2} and hence adequacy of ventilation.[1 2] However, whether or not this holds true for the COPA is unknown. With the COPA the cuff is opposed to the pharynx and the reliability of the seal is in doubt. Therefore, we have compared the differences between $P\text{E}'_{\text{CO}_2}$ and Pa_{CO_2} measured using a COPA or a TT in spontaneously breathing adults during general anaesthesia.

Methods and results

After obtaining approval from the Institutional Human Studies Committee of Teikyo University and informed consent, we studied 20 adult ASA I–II patients undergoing elective surgery. Exclusion criteria were history of cardiac or pulmonary abnormalities, abnormal airway anatomy or any condition which increased the risk of regurgitation of gastric contents or precluded the use of succinylcholine.

The study was designed to duplicate the within-group methods described by Chhibber, Kolano and Roberts.[3] Premedication was decided by the anaesthetist in charge. With subjects lying in the supine position, general anaesthesia was induced with propofol 2–3 mg kg^{-1} i.v. After establishing an adequate level of anaesthesia, the COPA was inserted, positioned and tested according to the manufacturer's instructions. The cuff was inflated with 30–40 ml of air. In general, sizes 9 and 10 were used for females and males, respectively. Head rotation to the side and neck extension were applied if necessary to ensure clinical airway patency.

Subjects were allowed to stabilize while breathing spontaneously a sevoflurane–oxygen mixture. Total fresh gas flow was set at 6 litre min^{-1}. When $P\text{E}'_{\text{CO}_2}$ had been stable for a minimum of 5 min, an arterial blood sample was obtained for measurement of Pa_{CO_2}, and $P\text{E}'_{\text{CO}_2}$ and tidal volume were recorded. The COPA was then removed and the trachea intubated with a TT after administration of succinylcholine 1–2 mg kg^{-1} i.v. Correct positioning of the TT was confirmed by capnography and auscultation of the chest to exclude endobronchial intubation. The TT used for females was 7.5 mm internal diameter (id) and for males 8.0 mm id. Subjects were allowed to recover from neuromuscular block and breathe spontaneously. Anaesthesia was maintained with sevoflurane in oxygen. After a minimum of 5 min of stable $P\text{E}'_{\text{CO}_2}$, a second blood sample was obtained for measurement of Pa_{CO_2}, and $P\text{E}'_{\text{CO}_2}$ and tidal volume were again recorded. During this period, no invasive procedures were performed and stable haemodynamic variables were maintained.

The respiratory gas was sampled at the Y connector and $P\text{E}'_{\text{CO}_2}$ was monitored with an infrared gas monitor (Ultima SV, Datex, Helsinki, Finland) which had been calibrated before each study. Its stated accuracy is ±0.15 kPa. The anaesthesia breathing system used was the adult non-rebreathing system with unidirectional valves. Tidal

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Table 1 Performance characteristics of the cuffed oropharyngeal airway (COPA) and tracheal tube (TT) (mean (SD)). $^*P<0.05$ compared with Pa_{CO_2}

	COPA	TT
Tidal volume (ml)	244 (89)	225 (66)
Ventilatory frequency (bpm)	23 (6)	24 (5)
$P\text{E}'_{CO_2}$ (kPa)	5.43 (0.55)*	5.96 (0.75)*
Pa_{CO_2} (kPa)	6.15 (0.64)	6.59 (0.84)
$Pa_{CO_2} - P\text{E}'_{CO_2}$ (kPa)	0.72 (0.45)	0.64 (0.40)

volume was measured with a spirometer (Respirometer RM121, Ohmeda, Mississauga, Ontario) placed at the end of the expiratory limb of the anaesthesia system. Arterial blood samples were analysed immediately with a Stat Profile 9 (Nova Biomedical, Waltham, MA). The analyser underwent two-point calibration before each study. Its accuracy is within 0.02 kPa and coefficient of variance is 3% for carbon dioxide.

Tidal volumes and ventilatory frequencies were analysed using a paired *t* test. Pa_{CO_2} and $P\text{E}'_{CO_2}$ data were compared using two-way analysis of variance with repeated measures.[4] A paired *t* test was performed to establish differences between arterial and end-tidal partial pressures with the COPA and TT. All values are mean (SD). $P<0.05$ was considered statistically significant.

We studied 20 patients (five males, 15 females), weighing 44–85 kg (mean 59.3 kg), aged 21–68 yr (mean 45.2 yr). Three patients were active smokers.

The results are summarized in table 1. There was no significant difference in tidal volume, ventilatory frequency, Pa_{CO_2} or $P\text{E}'_{CO_2}$ before and after intubation. As would be expected, Pa_{CO_2} was greater than $P\text{E}'_{CO_2}$ in all cases. The mean difference between Pa_{CO_2} and $P\text{E}'_{CO_2}$ with the COPA was 0.72 (0.45) kPa and with the TT 0.64 (0.40) kPa (ns; paired *t* test).

Comment

Differences between Pa_{CO_2} and $P\text{E}'_{CO_2}$ were 0.72 (0.45) kPa for the COPA and 0.64 (0.40) kPa for the TT, which are comparable with values obtained in previous studies.[1 2] As with the TT and LMA, the use of the COPA also allows $P\text{E}'_{CO_2}$ to function as a predictor of Pa_{CO_2}.

The use of within-group design excluded multiple confounding factors. Although the sample size in our study appeared to be small, power analysis demonstrated that our sample size had 98% power to detect a difference of 0.40 kPa or greater in $Pa_{CO_2} - P\text{E}'_{CO_2}$ between COPA and TT.[5] Therefore, the similarity in the differences between Pa_{CO_2} and $P\text{E}'_{CO_2}$ for the COPA and TT is unlikely to have resulted from a type II error.

We did not randomize the order of observations, but systematically made the COPA measurements first in order to avoid unnecessary tracheal intubation in surgical patients. This lack of randomization may lead to alteration of ventilation by administration of succinylcholine, stimulus of intubation and a longer anaesthetic when breathing through a TT. However, all respiratory variables (tidal volume, ventilatory frequency, Pa_{CO_2} and $P\text{E}'_{CO_2}$ were similar before and after intubation using repeated measures analysis of variance (table 1). The lack of randomization is not considered to have altered respiratory state.

The COPA is designed to be used in spontaneously breathing patients and the use of controlled ventilation via the COPA has not been reported. In common with the LMA, controlled ventilation via the COPA may place patients at increased risk of aspiration of gastric contents, as gases may be insufflated into the stomach. To avoid this risk of aspiration, we allowed subjects to breathe spontaneously.

In summary, in anaesthetized adults breathing spontaneously via a COPA, $P\text{E}'_{CO_2}$ was as useful in evaluating the adequacy of ventilation as when a TT was used.

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The blood–gas partition coefficient of xenon may be lower than generally accepted

T. Goto, K. Suwa, S. Uezono, F. Ichinose, M. Uchiyama and S. Morita

Summary

The blood–gas partition coefficients of xenon, reported more than 25 yr ago in the literature, vary considerably from 0.13 to 0.20. Consequently, we have determined this variable by directly injecting xenon-saturated blood into a gas chromatograph–mass spectrometer. This technique yielded a blood–gas partition coefficient for xenon of 0.115 (95% confidence interval 0.107–0.123). The solubility in water measured identically was 0.096, consistent with the reported value of 0.085. These data and a detailed review of the literature strongly suggest that the blood–gas partition coefficient of xenon may be lower than the generally accepted value of 0.14. (*Br. J. Anaesth.* 1998; **80**: 255–256)

Keywords: anaesthetics gases, xenon; solubility, partition coefficients

Xenon, an inert gas with anaesthetic properties (MAC = 71%), has recently attracted renewed interest because it possesses many of the characteristics of an ideal anaesthetic. Notably, it is extremely insoluble in human tissues, enabling faster induction of, and emergence from, anaesthesia than other inhalation anaesthetics.[1]

The blood–gas partition coefficient of xenon is generally accepted as 0.14.[2] However, the published values vary considerably from 0.13 to 0.20[3–8] and no study specifically documented a value of 0.14. Moreover, all of these measurements were performed more than 25 yr ago. Consequently, we have measured this variable by directly injecting xenon-saturated blood into a gas chromatograph–mass spectrometer. When analysing highly impure substances such as blood, addition of a mass spectrometer to a gas chromatograph results in more accurate identification and complete isolation of xenon because, while a gas chromatograph separates substances solely by the time required for each substance to pass through the column (i.e. retention time), a mass spectrometer further analyses these separated substances by determining their mass–charge ratios after ionization.

Methods and results

Blood (5 ml) was obtained from 10 healthy subjects (five males, five females, aged 21–54 yr). A sample of 2 ml was sent to the clinical laboratory for measurement of packed cell volume and plasma concentrations of albumin, cholesterol and triglycerides. The remaining 3 ml were immediately anticoagulated by adding citrate–phosphate–dextrose (CPD) 0.3 ml (containing per 100 ml: sodium citrate 2.63 g, citrate 0.327 g, glucose 2.32 g and $NaH_2PO_4 \cdot 2H_2O$ 0.251 g). To saturate blood with xenon, the specimen was placed in a 5-ml vial with an air-tight rubber top and stirred for 4 h at 37°C with 99.995% pure xenon (Nippon-Sanso, Tokyo, Japan) continuously flowing over it at a rate of 10 ml min^{-1}. Equilibration periods of 2, 3 and 4 h yielded similar partition coefficients.

Using an air-tight microsyringe, a 2-µl aliquot of each specimen was injected directly into a gas chromatograph (HP5890A, Hewlett Packard, USA) connected to a double-focusing mass spectrometer (AX-505W, JEOL, Tokyo, Japan). The chromatograph column was a 3 mm × 1 m stainless steel tube packed with molecular sieve 5A on 60/80 mesh, which was maintained at 100 °C. Helium was used as the carrier gas at a flow rate of 25 ml min^{-1}. As ^{129}Xe is the most abundant form of naturally occurring stable isotopes of xenon, we measured the area under the curve at the mass–charge ratio of 129 for 10 min after each injection. The mean and coefficient of variation (= SD/mean × 100%) of three measurements were determined for each sample. This mean was compared with the average area under the curve obtained from six injections (three before and three after injection of each specimen) of helium 2 ml containing xenon 10 ppm (Nippon-Sanso, Tokyo, Japan) to yield the solubility expressed as the volume of dry xenon gas dissolved in 1 ml of solvent at 37°C.

The mean solubility of xenon in anticoagulated blood was 0.112 (95% confidence interval 0.104–0.119). The median coefficient of variation was 8.5% (range 1.5–18.9%), implying that the measurements were precise. Solubilities in CPD solution and water were 0.073 and 0.096, respectively. The blood–gas partition coefficient for xenon, after correction for dilution of blood by the CPD solution, was estimated to be 0.115 (95% confidence interval 0.107–0.123) This correction was based on the assumption that (solubility in blood) × 3.0 = (solubility in the anticoagulated sample) × 3.3 − (solubility in the CPD

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Table 1 Published blood–gas (B/G) partition coefficients of xenon. GC=Gas chromatography; GC$_{133}$MS=gas chromatography–mass spectrometry; Xe=simultaneous measurements of ^{133}Xe radioactivities in gas and equilibrated blood; Hb=haemoglobin concentration. [a]Authors reported that the cell–plasma ratio of the blood sample was 1:2.0; [b] Calculated using a linear regression formula between solubility and packed cell volume; [c]Calculated using the measured plasma/gas and erythrocyte/gas partition coefficients; [d]mean (SD)

Author (year)	B/G partition coefficient	Method	Packed cell volume
DeBon and Featherstone (1964)[8]	0.20	GC	Not documented
Yeh and Peterson (1965)[3]	0.18	De-gassing	Hb = 14 g dl^{-1}
Muehlbaecher and colleagues (1966)[4]	0.149	GC	33%[a]
Rochester and colleagues (1967)[5]	0.134[b]	^{133}Xe	40%
Lagefoged and Anderson (1967)[6]	0.129[c]	^{133}Xe	40%
Kitani (1972)[7]	0.136[b]	^{133}Xe	40%
Goto and colleagues (this study)	0.115	GC-MS	40 (5)%[d]

solution) × 0.3, because 0.3 ml of the CPD solution were added to 3.0 ml of blood.

Mean packed cell volume and concentrations of albumin, cholesterol and triglyceride were 40.4 (SD 5.3)%, 45 (6) g $litre^{-1}$, 4.76 (0.80) mmol $litre^{-1}$ and 1.57 (0.59) mmol $litre^{-1}$, respectively.

Comment

Table 1 summarizes the published blood–gas partition coefficients for xenon. The oldest value of 0.20[8] is questionable because the same group of investigators later published a value of 0.149.[4] Yeh and Peterson[3] extracted dissolved xenon from saturated blood by repeated evacuation and obtained a value of 0.18. In contrast, lower and strikingly consistent values of approximately 0.13 were obtained by introducing radioactive xenon (^{133}Xe) into the gas space contacting the blood sample and simultaneously measuring the radioactivities in the gas and equilibrated blood.[5–7]

Our value of 0.115 determined by gas chromatography–mass spectrometry is estimated to contain an error of approximately ±0.01 because the coefficients of variation were less than 10% for most specimens and because solubility in water was determined as 0.096, approximately 10% higher than the value in the literature (0.085).[2] Thus our result appears to be consistent with those obtained using ^{133}Xe[5–7] but is significantly lower than other values.[3–4 8]

The reason for this discrepancy is unclear, but several possibilities warrant consideration. For example, the higher plasma lipid concentration of Yeh and Peterson[3] (total lipid 720 mg dl^{-1} in their study *vs* our concentrations of cholesterol of 184 mg dl^{-1} and triglyceride 137 mg dl^{-1}) might in part account for their larger value.[9] In contrast, although the solubility of xenon in blood increases linearly with packed cell volume,[5–7] our samples and those of other investigators had similar packed cell volume and haemoglobin concentrations (table 1). Finally, the difference in anticoagulants used (CPD solution compared with the more commonly used heparin) cannot be disregarded but is unlikely to be fully responsible because a larger amount of sodium citrate than we used has only a negligible effect on the solubility of volatile anaesthetics in blood.[10]

In summary, our measurement and a detailed review of the published literature suggest that the blood–gas partition coefficient of xenon may be lower than 0.14, the value currently most frequently cited.

Acknowledgement

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Sevoflurane has less effect than halothane on pulmonary afferent activity in the rabbit†

C. Moores, A. S. Davies and M. Dallak

Summary

We have compared the effects of sevoflurane and halothane on the discharge frequencies of 19 slowly adapting and four rapidly adapting lung receptors in the rabbit by recording from single vagal fibres. Both agents reduced the discharge frequency of slowly adapting receptors during expiration ($P<0.0005$), halothane having a greater effect than sevoflurane ($P<0.0005$). Neither agent had any effect on discharge frequency at the end of inspiration when discharge frequency is at a maximum. Neither agent affected the discharge frequency of rapidly adapting receptors. (*Br. J. Anaesth.* 1998; **80**: 257–259)

Keywords: anaesthetics volatile, sevoflurane; anaesthetics volatile, halothane; lung, receptors; rabbit

Lung receptors include slowly adapting (stretch) receptors (SAR), rapidly adapting (irritant) receptors (RAR) and J receptors. They form the afferent limbs of airway reflexes, including the Hering–Breuer reflex, reflex bronchoconstriction and the cough reflex.

The activity of these lung receptors has been shown to be influenced by volatile anaesthetic agents such as chloroform, ether,[1] halothane, isoflurane and enflurane.[2] Nishino, Anderson and Sant'Ambrogio found that the modern agents increased the firing threshold of SAR while at the same time increasing their discharge frequency above this threshold. They also found that increasing concentrations of volatile agents decreased the activity of RAR. They could not demonstrate a quantitative difference between the agents on either receptor type.[2]

To date, sevoflurane has not been studied. It differs from other volatile agents in that it appears to be much less irritating to the airway, being associated with a lower incidence of airway-protective reflexes.[3] It seems likely, therefore, that sevoflurane may also have a different effect on intrapulmonary receptors. In this study, we compared the effect of halothane and sevoflurane on the activity of intrapulmonary receptors measured from single vagal fibres in rabbits undergoing ventilation.

Methods and results

After obtaining approval from the Home Office, we studied four New Zealand White rabbits. Each was anaesthetized with 25% urethane 7 ml kg^{-1}. The femoral vein was cannulated to allow i.v. injections, and the femoral artery was cannulated for measurement of arterial pressure and heart rate. The trachea was cannulated, the rabbit paralysed with vecuronium 0.2 mg kg^{-1} and its lungs ventilated with air using a tidal volume of 6 ml kg^{-1} and a ventilatory frequency of 80 bpm to maintain end-tidal carbon dioxide partial pressure close to the level measured before ventilation. Airway flow was measured using a pneumotachograph, the flow signal being integrated electronically to give volume (CS5, Griffin). End-tidal concentrations of anaesthetic gas and carbon dioxide were measured continually (Capnomac Ultima, Datex).

Both vagi were divided in the neck to prevent reflex bronchoconstriction which may influence SAR activity. The distal end of the left vagus was desheathed and divided into thin filaments. Recordings were made from these filaments using bipolar platinum electrodes and nerve discharges were displayed on an oscilloscope and fed to a loudspeaker. Further subdivision of each filament continued, until a filament was found containing a single active nerve fibre from a pulmonary afferent. The single fibre was identified as originating from either a pulmonary stretch receptor or rapidly adapting receptor on the basis of its pattern of firing during the respiratory cycle and its response to short pulses of either positive or negative pressure.

The lungs were ventilated with oxygen for 2 min and then either sevoflurane or halothane was introduced at a concentration of 2% for 1 min followed by 5% for 1 min. The rabbit's lungs were then ventilated with oxygen for 2 min. Thereafter, 2% and 5% of the second agent was introduced as for the first. The vagal filament was then discarded, another filament was dissected from the vagus and the procedure repeated. The order in which the volatile agents were used was reversed in consecutive procedures.

Nerve impulses were converted into 5-V electronic pulses using a windows discriminator (Neurolog, Digitimer Ltd). Airway flow and pressure, tidal

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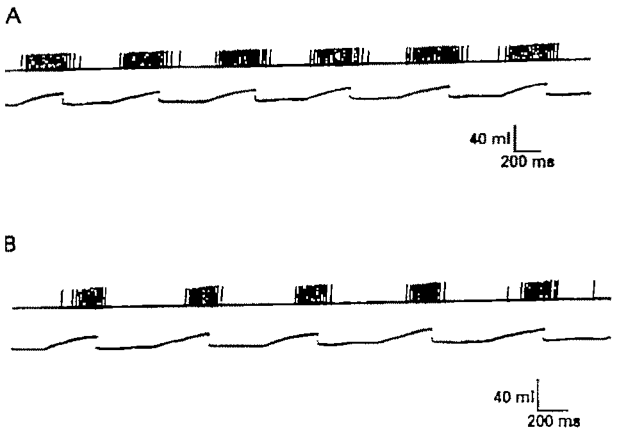

Figure 1 A: Slowly adapting receptor activity and inspired volume during control conditions. The upper trace shows 5-V processed nerve impulses and the lower trace inspired volume (integrated flow signal). Receptor activity increased with increasing lung volume and decreased to a minimum during expiration. B: Impulses from the same receptor exposed to 5% halothane. The threshold at which firing commenced was higher, but the maximum rate of firing was unchanged.

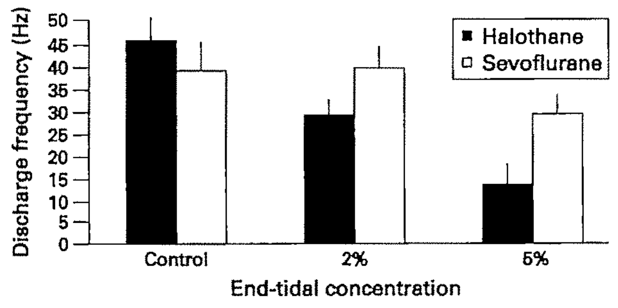

Figure 2 Mean (SEM) discharge frequency of slowly adapting receptors during expiration. Concentration effects and difference between agents were significant ($P<0.0005$).

volume, arterial pressure and nerve impulses were recorded onto eight-track magnetic tape (XR30, TEAC). Statistical analysis was performed using repeated measures ANOVA (SPSS for Windows.)

Recordings were made from 23 single fibres: 19 from SAR and four from RAR.

SLOWLY ADAPTING RECEPTORS

Figure 1A shows the characteristic discharge pattern of an SAR during the respiratory cycle. With increasing lung volume the discharge frequency of the receptor increases. Figure 1B illustrates the discharge pattern of the same receptor during administration of 5% halothane. This receptor ceases to discharge for a period during expiration; however, some receptors discharged throughout the respiratory cycle, and therefore separate analysis of discharge frequency during inspiration and expiration was necessary, rather than analysis of the duration of discharge of the receptors.

Expiration

During expiration, the effect of both halothane and sevoflurane is to reduce the receptor discharge frequency. Figure 2 demonstrates the effect of increasing concentration on receptor discharge frequency during expiration, when discharge frequency is at a minimum. The decrease in discharge frequency with increasing concentration was significant ($P<0.0005$). Halothane had a significantly greater effect than sevoflurane in reducing discharge frequency during expiration ($P<0.0005$).

Inspiration

During inspiration, we were unable to demonstrate any effect of either agent on receptor discharge frequency. Mean discharge frequency during the final 100 ms of inspiration for halothane was 107.7 (SEM 6.5) Hz (control) and 106.7 (7.2) Hz (5% end-tidal concentration), and for sevoflurane 103.5 (7.0) Hz (control) and 114.5 (7.1) Hz (5% end-tidal concentration).

RAPIDLY ADAPTING RECEPTORS

During the course of this investigation, we recorded from only four RAR as these receptors form a small proportion of the lung receptors in the rabbit. Measurements of nerve discharge frequency were averaged over a 5-s period. At the concentrations used, we found no significant effect of either agent on the discharge frequency of the RAR. Mean discharge frequency for halothane was 6.1 (SEM 1.9) Hz (control) and 6.7 (1.7) Hz (5% end-tidal concentration), and for sevoflurane 5.6 (1.9) Hz (control) and 7.7 (1.2) Hz (5% end-tidal concentration)

In the case of two receptors, we recorded airway pressure. There was no significant change in maximum airway pressure during ventilation with either volatile agent, suggesting that they did not cause a significant degree of bronchodilatation which may have altered SAR activity. Mean maximum airway pressure during ventilation for halothane was 1.39 (SEM 0.1) cm H_2O (control) and 1.49 (0.1) cm H_2O (5% end-tidal concentration), and for sevoflurane 1.39 (0.1) cm H_2O (control) and 1.44 (0.1) cm H_2O (5% end-tidal concentration).

Comment

We have shown that the predominant effect during expiration of halothane and sevoflurane is to decrease the discharge frequency of SAR. This represents an increase in the discharge threshold of the receptors, and confirms the findings of Nishino, Anderson and Sant'Ambrogio using halothane, isoflurane and enflurane.[2] Nishino, Anderson and Sant'Ambrogio did not demonstrate a significant quantitative difference between the effect of these agents on SAR; we found that halothane had a significantly greater effect than sevoflurane on the discharge frequency of SAR during expiration. Sevoflurane has less effect than other agents on upper airway receptors, as manifest by its low level of airway irritability, and it is interesting that it also had less of an effect on lung SAR.

We did not demonstrate an effect of either volatile agent on the discharge frequency of SAR at the end of inspiration when their firing rate is at a maximum. Other workers have found in decerebrate cats that the modern agents sensitize these receptors above their firing threshold.[2] It is possible that had we used larger tidal volumes, applying a greater stimulus to these receptors, their discharge frequency at end-expiration may have been influenced by the volatile agents.

SAR form part of the Hering–Breuer inflation reflex which in animals is important for the control of breathing pattern.[4] Halothane and sevoflurane produce tachypnoea in animals and humans.[5 6] The increase in ventilatory frequency that is seen in animals during anaesthesia with halothane is smaller after vagotomy,[7] suggesting that changes in lung afferent activity are partly responsible presumably via the Hering–Breuer reflex. In both animals and humans, tachypnoea during anaesthesia with sevoflurane is less than that with halothane and vagotomy does not alter the increase in ventilatory frequency that sevoflurane causes in decerebrate cats.[7] It is possible that the differences between halothane and sevoflurane in animals may be caused by differences in the sensitivity of SAR to the two agents, although a central cause cannot be excluded. Although in anaesthetized humans there is little evidence that the Hering–Breuer reflex is important in modulating eupnoeic breathing,[8 9] the effect of volatile agents on lung receptors could possibly result in the modulation of other airway reflexes, such as the cough reflex, reflex bronchodilatation and bronchoconstriction.

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CASE REPORT

Propofol and electroconvulsive therapy in a patient at risk from acute intermittent porphyria

I. H. SHAW AND I. G. MCKEITH

Summary

A severely depressed 57-yr-old woman at risk from acute intermittent porphyria presented for a course of electroconvulsive therapy. With propofol as the induction agent the course of electroconvulsive therapy was both uneventful and successful. (*Br. J. Anaesth.* 1998; **80**: 260–262)

Keywords: anaesthetics i.v., propofol; brain, electroconvulsive therapy; complications, porphyria

Acute intermittent porphyria (AIP) may be induced in susceptible patients by several commonly used anaesthetic drugs.[1] Isolated case reports suggest that propofol may be a safe alternative in such patients. Propofol has also been reported to reduce the duration of seizure activity during electroconvulsive therapy (ECT) and as a consequence doubts have been expressed about the efficacy of ECT after anaesthesia with propofol.[2 3]

Case report

A 57-yr-old woman suffering from Parkinson's disease presented with a major depressive disorder as part of an organic affective syndrome. She had paranoid and nihilistic delusions and was refusing food and fluids. As these symptoms had failed to respond to drug therapy ECT was felt to be the only alternative. The patient was a member of a large family with a history of autosomally dominant AIP.

Her red blood cell porphobilinogen deaminase (PBG-D) activity was abnormally low (12.7 nmol porphyrin formed/ml erythrocytes/h; normal range 30–54) confirming that she too had AIP. Urinary porphyrins were normal. The patient gave no history of having suffered from a symptomatic episode of AIP.

At the preanaesthetic assessment the woman, who weighed 45 kg, was noted to be tremulous, bradykinetic and rigid, consistent with Parkinson's disease. She was normotensive and no abnormality was found on cardiorespiratory examination, but the ECG indicated changes consistent with an old anteroseptal myocardial infarction. The patient denied having suffered from cardiorespiratory symptoms. Apart from borderline hypokalaemia, all routine laboratory investigations were normal. Her current medication was pergolide, cobeneldopa, benzhexol, thyroxine and lofepramine.

A total of seven ECT treatments were administered in the ECT suite over a period of 23 days. ECG, arterial pressure and oxygen saturation were monitored routinely. After 1 min of preoxygenation with 100% oxygen, anaesthesia was induced with propofol and neuromuscular block facilitated by succinylcholine. Bilateral ECT was administered after a brief period of hyperventilation with 100% oxygen and seizure duration was timed from application of the current (table 1).

In our patient mean seizure time was 31 (range 16–55) s and aggregate seizure duration was 218 s. The patient was monitored during recovery while breathing 35% oxygen. Administration and conduct of all seven treatments was uneventful. In total, the patient had received propofol 450 mg (mean induction dose 64 (range 60–80) mg) over a 23-day period.

No urinary porphyrins or blood porphobilinogen were detected when measured on day 14 after the fourth treatment. During the course of the ECT the patient remained an inpatient on a neurological ward where the staff were particularly vigilant for signs and symptoms of AIP. At no time did the patient's neurological condition give cause for concern. At the end of treatment her mood had returned to normal with full remission of her psychotic symptoms.

Discussion

The porphyrias are a group of uncommon inherited metabolic disorders in which there is a disturbance of haem synthesis. In AIP a deficiency of porphobilinogen deaminase (PBG-D) results in the accumulation of the intermediate metabolites porphobilinogen (PBG) and animolaevulinic acid (ALA). AIP can be induced by many drugs familiar to the anaesthetist, in particular the barbiturate induction agents.[1 4] Clinically, symptoms may be severe and of rapid onset. Abdominal pain, paralysis, mania, coma and death can ensue.

In recent years conflicting reports have appeared in the literature on the porphyrogenicity of propofol. Several reports have shown that a single induction dose had no adverse clinical effect.[5–7] Mitterschiffthaler and colleagues[8] reported the safe use of

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Table 1 Current applied, seizure duration and anaesthetic drugs administered during the course of ECT given to our patient with acute intermittent porphyria. *Porphobilinogen and urinary porphyrins were measured after treatment No. 4

Treatment No.	Day	Current administered (mA bilateral)	Seizure duration (s)	Propofol dose (mg)	Succinylcholine dose (mg)
1	1	400	55	80	40
2	7	400	20	70	40
3	9	500	16	60	35
4*	12	500	45	60	35
5	18	500	25	60	35
6	21	500	35	60	35
7	23	500	22	60	35

propofol on two occasions in a susceptible patient within a 2-week period, and Harrison and McAuley[9] successfully sedated a patient with symptomatic life-threatening AIP for 32 days in intensive care. An *in vivo* rat model failed to find any evidence of the porphyrogenicity of propofol.[10] Increase in urinary porphyrins after propofol anaesthesia has been reported in susceptible patients.[11 12] On one occasion this was only after a third propofol anaesthetic. In both reports patients remained asymptomatic and anaesthesia was otherwise uneventful. Kasraie and Cousins[13] reported a patient who was readmitted with an acute symptomatic attack of coproporphyria 4 days after propofol anaesthesia. However, the patient had also been exposed to several other potentially porphyrogenic drugs, the significance of which is uncertain.

Our patient received seven propofol anaesthetics over a 23-day period without biochemical or clinical evidence of induced AIP. Of interest is Kauppinen and Mustajoki's[14] findings that patients with AIP who have never experienced any symptoms, particularly if they have low concentrations of urinary porphyrin precursors, appear to tolerate precipitating drugs well. The authors proposed a more permissive attitude to the administration of potentially porphyrogenic drugs in previously totally asymptomatic patients. In those patients known to have had a previous attack, the exclusion of such drugs was regarded as mandatory. Our patient had been asymptomatic all her life.

One concern expressed in previous isolated case reports is that not every administration of a porphyrogenic drug induces porphyria and consequently many reports have concluded with a warning about the use of propofol in patients at risk from acute porphyria[11-13] and that perioperative biochemical monitoring should always be carried out. For a detailed discussion of anaesthesia for the porphyric patient the reader should consult the review by Harrison, Meissner and Hift.[1]

For a course of ECT to be effective a minimum aggregate seizure duration is thought to be necessary.[15] Preoxygenation and ventilation with 100% oxygen during ECT has been shown to prolong seizure duration,[16] as has hypocapnia induced by passive hyperventilation.[17] Several reports have been published which show that propofol anaesthesia reduces seizure duration[2 3 18 19] and as a consequence the manufacturers have recommended that propofol is unsuitable for use in ECT.

Avramov, Husain and White[20] demonstrated a dose-dependent decrease in seizure duration with both methohexital and propofol. The authors concluded that induction doses of propofol in excess of 1.5 mg kg^{-1} significantly reduced seizure duration. Smaller doses of propofol in the range 0.75–1.0 mg kg^{-1} were similar to commonly used doses of methohexital. Our patient received propofol in the dose range 1.3–1.7 mg kg^{-1}. In another comparative study,[19] seizure duration was also reduced after propofol. The efficacy of ECT was found to be unaffected by the choice of propofol as the anaesthetic induction agent compared with methohexital. This finding was also observed by Kirkby and colleagues.[21]

A seizure duration of more than 25 s is often quoted as being necessary for ECT.[22] However, observed seizure duration is usually less than that demonstrated by simultaneous EEG recording. On this basis, with the exception of the third treatment, most of our patient's seizure times could be regarded as adequate. The aggregate seizure duration over seven treatments was sufficient to bring about a beneficial clinical response. The crucial test as regards the efficacy of ECT is whether the patient responds to the treatment as expected.[22]

Our patient with AIP had an uneventful and successful course of ECT using propofol as the anaesthetic agent. The barbiturate anaesthetic methohexital is still regarded by many as the anaesthetic agent of choice for ECT. The known porphyrogenicity precluded its use in our patient. Ketamine, an anaesthetic known to be safe in porphyria, was felt to be particularly unsuitable for ECT in our patient because of its known hallucinogenic effects.

Unfortunately, approximately 9 months later the patient had a relapse of her depressive illness necessitating a further course of ECT. Again propofol was used as the induction agent with success and without ill effect.

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Commentary

Mapleson WW. The elimination of rebreathing in various semi-closed anaesthetic systems. *British Journal of Anaesthesia* 1954; **26**: 323–332.

The first anaesthesia breathing systems were developed for delivery of nitrous oxide–oxygen mixtures for dental anaesthesia. While some of the earlier machines used wide bore tubing to connect the machine to the patient, most used a 1–2-m length of narrow bore tubing to transfer the gas mixture to the reservoir bag and expiratory valve which were situated close to the face mask. Both the Gwathmey–Woolsey apparatus of 1912 and the close copy introduced by Boyle at the beginning of World War 1 used this arrangement. However, when Magill was anaesthetizing for reconstructive surgery after the war, he found that the presence of the bag close to the patient's face interfered with the work of the plastic surgeon, and therefore he moved the bag to the machine end of the connection tubing. By this time Magill was moving from insufflation anaesthesia to the use of a wide bore tracheal tube, and this made him realize that the connecting tubing would have to be of wide bore to reduce the resistance to breathing. The supply problem was solved initially by using corrugated tubing from First World War gas masks to connect the bag to the expiratory valve. Although the to and fro carbon dioxide absorption system was introduced by Waters in 1924 and the circle carbon dioxide absorption system followed in 1930, these systems were never used widely in the UK, their use tending to be restricted to situations where cyclopropane was required. For most other applications the Magill system retained its popularity in the UK for more than 50 yr.

When Mapleson was appointed to the post of physicist in the Cardiff department he found that anaesthetists were using several different semi-closed systems and to reduce confusion, he classified these alphabetically. "A" was the standard Magill breathing system with a tube of approximately 22 mm internal diameter and an internal volume of approximately 500 ml. "B" was a system made by Medical and Industrial Equipment Ltd which appeared to be similar to the "A" system, but in which fresh gas flow was diverted from the machine common outlet through a narrow bore tube to rejoin the breathing system by the expiratory valve. It was claimed that this arrangement enabled inspired gas concentrations to be changed rapidly, and that it decreased rebreathing, but as Mapleson's diagram showed, the metal diaphragm in the bag mount which diverted the gas flow into the narrow bore tube caused the corrugated tube and reservoir bag to become one large rebreathing chamber. The "C" system was that used on the original Boyle's machine, but in 1954 it would have been produced by removing the carbon dioxide absorption canister from the Water's to and fro system. Such a system was used frequently for transport or resuscitation of patients in the days before self-inflating bags and reliable non-rebreathing valves were available. System "E" was the Ayre's T-piece, introduced for paediatric anaesthesia in 1937, and system "D" was the Jackson Rees modification used with controlled ventilation.

In the 1950s most anaesthetists using the Magill system set flowmeters to deliver 2 litre of oxygen and 5 litre of nitrous oxide, although there was little evidence to support this choice. Molyneux and Pask had used a primitive pneumotachograph to record flows on the patient side of the reservoir bag and had concluded that much higher flows were needed to prevent rebreathing.[1] However, Mapleson concluded from his theoretical analysis that rebreathing would be prevented if fresh gas flow was greater than alveolar ventilation. This definition of rebreathing recognized that re-inhalation of gas which had come from the apparatus and patient's deadspace (and which therefore did not contain carbon dioxide) had no effect on gas exchange. In order to render the mathematics simple enough for the average anaesthetist to understand, Mapleson made five simplifying assumptions. These were examined in detail, and although none appeared likely to have a gross effect on the prediction, Mapleson cautiously modified his conclusion and stated that rebreathing of carbon dioxide-rich gas would be prevented completely if the fresh gas flow rate exceeded the patient's minute volume with system A, and that a flow rate approximating to twice the patient's minute volume was required with the other systems.

Mapleson's prediction that there would be no rebreathing with the "A" system if fresh gas flow exceeded minute volume was soon confirmed by experiments on lung models and observations in the operating theatre, but it was not until 1967 that Kain and Nunn confirmed in anaesthetized patients that fresh gas flow could be reduced to approximately 70% of minute volume before rebreathing occurred.[2]

In the 1950s the "A" system was used frequently when assisting or controlling ventilation during short operations such as appendicectomy. Under these circumstances a mixture of fresh and expired gas is discharged from the valve during inspiration. This results in a variable degree of rebreathing.[3] Waters and Mapleson went on to provide a theoretical analysis of the performance of systems "A", "B", "C" and "D" during controlled respiration and concluded that system "A" was the least efficient.[4] However, their observations in five patients indicated that end-tidal $P\text{CO}_2$ could be maintained within normal limits with all four systems when fresh gas flow was increased to 8 litre min^{-1}.

Mapleson's clear analysis of the dynamics of these breathing systems shows how important it is for the anaesthetist to have an understanding of simple physics and mathematics. It has also stimulated others to design breathing systems which preferentially dump the carbon dioxide-containing moiety of expired gas, and so decrease fresh gas requirements. But, above all, this article marked the arrival on the anaesthetic scene of one who has made many major contributions to our knowledge of the scientific basis of anaesthesia. It is a pleasure to acknowledge his selfless devotion to our specialty.

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THE ELIMINATION OF REBREATHING IN VARIOUS SEMI-CLOSED ANAESTHETIC SYSTEMS

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INTRODUCTION

A VALUABLE theoretical and experimental analysis of the flow of gases in a semi-closed anaesthetic system was published by Molyneux and Pask in 1951. Their theoretical analysis was applied to one particular type of system and involved the assumption of certain idealized characteristics of the expiratory valve and of the breathing pattern. In the present work it is proposed to extend the theoretical analysis to other types of semi-closed systems and to take account of the effects of the actual characteristics of the expiratory valve and reservoir bag and of breathing patterns other than the idealized one.

In all, five systems will be considered (A, B, C, D, E in figure 1) of which A was analyzed by Molyneux and Pask.

SYSTEM A

Expiratory valve close to face mask, separated by corrugated tube from reservoir bag and supply of fresh gases.

In this simple analysis the following assumptions will be made:

(1) Gas enters the system from the anaesthetic machine at a constant volume flowrate F_a.

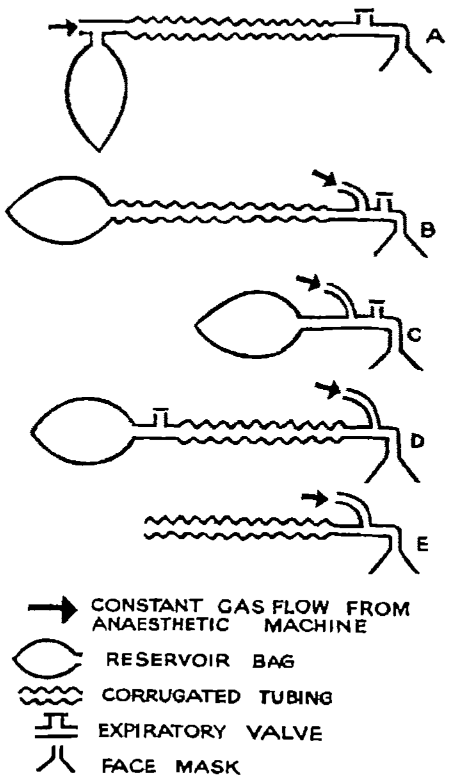

Fig. 1

The five semi-closed anaesthetic systems.

(2) At the start of inspiration the flow-rate into the lungs rises instantaneously to some value greater than F_a. No other assumption need be made as to the nature of the breathing pattern.

(3) The expiratory valve opens when the pressure in the system exceeds some critical value slightly above atmospheric and the valve will pass large flows without further increase in the pressure drop across it.

(4) The system is in a stable state—that is to say the conditions at any particular moment in the cycle of respiration are constant from one respiration to another.

(5) "Plug" flow occurs in the corrugated tubing, face mask and patient's trachea—that is, no longitudinal mixing occurs in these regions.

During expiration gases will enter the system at a known constant rate, F_a, from the anaesthetic machine and an unknown varying rate, say f_r, from the patient. Initially the fresh anaesthetic gases will flow directly into the bag while the expired gases will flow back along the corrugated tubing, forcing gas from the tubing into the bag. When the bag volume rises to some critical value, say V_c, at which the pressure inside it is equal to the opening pressure of the expiratory valve, the valve will open. Then, in virtue of assumption 3, the pressure in the system will not rise further and the volume of the bag will remain constant at V_c. The expired gases will flow directly out through the valve at an unknown varying rate which may still be represented by f_r, while the fresh anaesthetic gases will flow forward along the corrugated tubing still at the known constant rate F_a, forcing out through the expiratory valve gas which had previously entered the corrugated tube from the patient at the beginning of expiration. Apart from the variation of f_r conditions will then remain constant until the start of inspiration.

At the start of inspiration, in virtue of assumption 2, gas will be drawn from the system by the patient faster than it enters from the anaesthetic machine. The additional gas must necessarily be drawn from the reservoir bag whose volume will therefore decrease. Immediately this volume reduction starts there will be a corresponding reduction in the pressure in the system (Mapleson, 1954) below the opening pressure of the expiratory valve which will consequently close immediately inspiration begins. Thereafter conditions will remain steady, the bag slowly emptying, until the rate of inspiration, f_r, falls below the rate of supply of fresh gases, F_a, when the bag will begin to refill. When expiration commences the bag will fill comparatively rapidly in the manner described at the beginning of this analysis.

Now let V_t = patient's tidal volume.

T_1 = time from the start of one inspiration to the end of the same inspiration.

T_2 = time from the end of one inspiration to the start of the next inspiration.

T = duration of one complete respiratory cycle = $T_1 + T_2$.

T' = time from the end of inspiration to the opening of the expiratory valve.

Then the volume drawn from the bag during inspiration will be $V_t - F_a T_1$.

This volume is replaced during expiration in a time, T'. A portion, $F_a T'$, will come direct from the anaesthetic machine, while the remainder, $V_t - F_a T_1 - F_a T'$, will come from the patient. This last volume, $V_t - F_a T_1 - F_a T'$, is thus the volume of expired gas which enters the corrugated tubing and, at the instant at which the valve opens, will reside in the right-hand end of the tube (fig. 1, A), assuming, as one reasonably may in all normal circumstances, that this volume is less than the volume of the corrugated tubing. During the remainder of the time $T_2 - T'$ before the next inspiration, a volume, $F_a T_2 - F_a T'$, of fresh anaesthetic gas will enter the corrugated tubing from the machine at the left (fig. 1, A) and drive out through the expiratory valve at the right an equal volume of the expired gases residing in the right-hand end of the tubing. At the start of the next inspiration, therefore, the volume of expired gas still remaining in the corrugated tubing will be $V_t - F_a T_1 - F_a T' - F_a T_2 + F_a T' = V_t - F_a T$. However, this volume will be composed of gas which was breathed out at the beginning of expiration. Therefore, provided this volume does not exceed V_d, the dead space of the patient plus mask, it will not contain any gas which has been in contact with the alveoli of the lungs—that is to say, it will not contain any "contaminated" gas. Thus a criterion for the elimination of rebreathing may be expressed mathematically by:

$$V_t - F_a T \leqslant V_d$$

or

$$F_a \geqslant (V_t - V_d)/T \text{..........} (1)$$

Now V_t/T is one tidal volume divided by the period of one respiratory cycle and consequently is equal to the minute volume.* Similarly, $(V_t - V_d)/T$ may be referred to as the "effective" minute volume, since it is equal to the average rate of supply of fresh gases to the alveoli of the lungs. Then the criterion for the elimination of rebreathing may be expressed in words by:

> "The volume flowrate of anaesthetic mixture must be not less than the patient's effective minute volume."

It will be realized that this criterion is considerably at variance with that established by Molyneux and Pask. This is due, of course, to the different assumptions made in the present analysis. It is now proposed to examine the effect of various inaccuracies involved in some of these assumptions.

Assumption 5 clearly represents a highly idealized state of affairs; some longitudinal mixing is bound to occur in the system so that when equation (1) is just satisfied some "contaminated" expired gas will, in fact, still reside in the corrugated tubing at the beginning of inspiration and will consequently be rebreathed. In order to *ensure* the elimination of rebreathing, therefore, the criterion:

$$F_a \geqslant V_t/T \text{..............} (2)$$

might be adopted. That is to say that the flow of fresh gas must be not less than the patient's actual minute volume. It imposes the condition that in the absence of mixing none of the gas from the previous expiration shall remain in the system at the start of inspiration. Since mixing will occur some small volume of expired gas will in

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* Minute volume (F_m) = tidal volume (V_t) × number of respiratory cycles per minute (n). Now, $n = 1/T$ (T in minutes); therefore, $F_m = V_t/T$.

fact remain (an equal volume of fresh gas having escaped through the expiratory valve to maintain the balance) but it will probably consist mainly of gas which has not been in contact with the alveoli of the lungs. Molyneux and Pask took an even stricter condition: namely, that the volume of expired gas which *initially* flows back into the corrugated tube shall not exceed the total deadspace. That is to say

$$V_t - F_a (T_1 + T') \leqslant V_d$$

or

$$F_a \geqslant (V_t - V_d) / (T_1 + T') \text{.....} (3)$$

Even with this condition, however, it is still just possible that mixing would lead to some small amount of rebreathing. In the limit, therefore, it could be assumed that rebreathing will be completely eliminated only if no expired gas is allowed to enter the corrugated tube at any time. That is to say $V_t - F_a (T_1 + T') \leqslant O$ or, since in this condition T' must equal O

$$F_a \geqslant V_t/T \text{..............} (4)$$

(If the periods of inspiration and expiration are equal this is equivalent to saying that the flow of fresh gases must be at least equal to twice the actual minute volume.) If no mixing occurred a graph of percentage rebreathing against the ratio F_a/F_m where F_m is the actual minute volume would appear somewhat as the solid line of figure 2. With mixing, the graph would be modified to something like that shown by the dotted line in the same figure. It would appear that the only way to determine the exact nature of the dotted line would be to perform rapid continuous gas analysis within the semi-closed system. Until this is done and until an acceptable minimum percentage of rebreathing is agreed, it seems that the choice of the condition to establish a criterion for the effective elimination of rebreathing is largely arbitrary. In the author's opinion, quite a small increase in the flow of fresh gases above the minimum required by equation (1) would probably be sufficient to reduce the amount of rebreathing to an acceptably low level.

Instead of making assumption 2, let account be taken of the measurements of Proctor and Hardy (1949), which show that with a patient inspiring against negligible resistance (which will be the case in these semi-closed systems) the inspiratory flowrate increases gradually (though rapidly), and not instantaneously, at the beginning of inspiration. Thus there will be some short period of duration, say T_3, at the beginning of inspiration during which the inspiratory flowrate will be less than the flow of fresh gas from the machine. During this period, therefore,

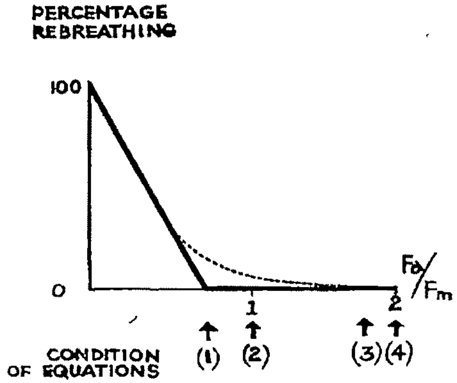

FIG. 2

Graph of percentage rebreathing against the ratio F_a/F_m (flowrate of fresh gases over patient's minute volume) for system A. Solid line: theoretical curve in the absence of longitudinal mixing. Broken line: assumed curve in the presence of mixing some of the gas in the right-hand end of the tube will enter the patient and some will leave through the expiratory valve. This state of affairs will persist until the inspiratory flowrate exceeds F_a when the valve will shut and the bag volume begin to decrease.

During this period a volume of gas, $F_a T_3$, will flow from the anaesthetic machine. If the rate of increase of inspiratory flow is constant during this period, half of this volume, namely $F_a T_3/2$, will enter the patient, and half will leave through the expiratory valve. Now during the remainder of the inspiration the patient will draw the remainder of the tidal volume, $V_t - F_a T_3/2$, and the anaesthetic machine will supply a volume, $F_a(T_1 - T_3)$ of fresh gas. The difference, $V_t - F_a T_1 + F_a T_3/2$, will be drawn from the bag. At a time T' after the end of inspiration, the bag will have regained its critical volume V_c, $F_a T'$ coming from the anaesthetic machine and the remainder, $V_t - F_a(T_1 - T_3/2 + T')$, coming from the patient's expiration (into the right-hand end of the corrugated tube). During the rest of the time up to the start of inspiration $(T_2 - T')$ a volume, $F_a(T_2 - T')$, of fresh gas will enter the left-hand end of the tube, driving out through the expiratory valve all but $V_t - F_a(T_1 - T_3/2 + T') - F_a(T_2 - T') = V_t - F_a(T - T_3/2)$ of the patient's expiration. Then, assuming that no longitudinal mixing occurs, it is this volume which must contain no "contaminated" expired gas if rebreathing is to be eliminated.

That is $V_t - F_a(T - T_3/2) \leqslant V_d$

or $F_a \geqslant (V_t - V_d)/(T - T_3/2)$......(5)

From the graphs given by Proctor and Hardy it is apparent that, when F_a is about equal either to the effective or to the actual minute volume of the patient, T_3 is only about a tenth of T so that equation (5) differs only by a twentieth or a factor 1.05 from equation (1) and it is apparent that assumption 2 introduces no appreciable error.

Now let assumption 3 be modified to take account of the increase in pressure drop across the valve which occurs with an increase of flow through the valve (Mushin and Mapleson, 1954). Let the expiratory valve close at a time, T_4, after the start of inspiration and during this period let the patient inspire a volume, V_p. When the valve closes the bag volume will be V_c and therefore at the end of inspiration it will be say, $V_1 = V_c - \{V_t - V_p - F_a(T_1 - T_4)\}$. Let the bag volume at the beginning of inspiration be V_2. Then the net flow of expired gas into the corrugated tube will be $V_2 - V_1 - F_a T_2 = V - V_c + V_t - V_p - F_a(T - T_4)$. This must be not greater than V_d for the elimination of rebreathing, in the absence of mixing. Therefore

$$F_a \geqslant \frac{V_t - V_d + (V_2 - V_c - V_p)}{T - T_4} \quad .....(6)$$

In order to allot numerical values to the quantities $(V_2 - V_c - V_p)$ and T_4 it is necessary to assume some definite shape for the respiratory flowrate curve and to apply a somewhat lengthy mathematical analysis which it is felt would be somewhat out of place here. However, it can be shown that under all conditions of respiration and valve and bag characteristics likely to be encountered in clinical practice the minimum value required for F_a in order to eliminate rebreathing while being, of course, greater than $(V_t - V_d)/T$ (the effective minute volume) will not be so great as V_t/T (the actual minute volume).

Assumptions 1 and 4 merely restrict the applicability of the analysis to steady conditions.

Thus it seems probable that the errors introduced by assumptions 2, 3 and 5 could be allowed for by adopting equation 2 rather than equation 1. That is to say that it is probably safe to assume that in system A rebreathing of gas which has been in contact with the alveoli of the lungs will be almost completely prevented if the flow of fresh anaesthetic gas is at least equal to the patient's minute volume.

SYSTEM B

Expiratory valve and supply of fresh gases close to face mask, separated by corrugated tube from reservoir bag.

The same assumptions will be made here as for system A. Some time during expiration the bag will fill to the critical volume V_c, and the expiratory valve will open, fresh gas passing directly out at a rate F_a and expired gas at f_r. At the start of inspiration the valve will close and gas will enter the patient at a rate F_a from the machine and a rate $f_r - F_a$ from the corrugated tubing and bag until the full tidal volume V_t has been drawn. Then, at the start of expiration, fresh gas will flow at a rate F_a and expired gas at a rate f_r back along the corrugated tube until the bag volume again reaches V_c and the valve again opens.

Now the volume drawn from the corrugated tube and bag during inspiration $= V_t - F_a T_1$. Of this, $F_a T'$ will be replaced by fresh gas and the remainder, $V_t - F_a T_1 - F_a T'$, by expired gas. This gas will remain in the corrugated tube until inspiration begins since, when the expiratory valve is open, the fresh gases will leave directly through it instead of displacing expired gas from the tube as in system A.

Thus the amount of gas which will be rebreathed is $V_t - F_a T_1 - F_a T'$. Since this rebreathed gas entered the corrugated tubing at the start of expiration, it may be assumed that the rebreathing of contaminated gas will be eliminated if

$$V_t - F_a T_1 - F_a T' \leqslant V_d$$

that is, if $F_a \geqslant (V_t - V_d)/(T_1 + T')$...(7)

Now unless some assumption is made as to the form of the expiratory flowrate curve, T' is indeterminate. However, it must be less than T_2 and therefore $T_1 + T'$ must be less than T. Thus to eliminate rebreathing the flow of gases from the anaesthetic machine must exceed some value which itself is appreciably greater than the patient's effective minute volume. Thus a higher flowrate is needed in this system than in system A.

As in system A, equation (7) holds good only on the assumption (No. 5) that no mixing occurs in the patient's trachea and the face mask. If mixing is assumed to occur there, then the volume of expired gas which is permitted to enter the corrugated tube must be more severely restricted and in the limit *no* expired gas can be permitted to enter it. That is to say, $V_t - F_a T_1 - F_a T' \leqslant O$. Since T' must now equal O,

$$F_a \geqslant V_t/T_1 \quad ....(8)$$

Remembering that V_t/T is the patient's minute volume and that the measurements of Proctor and Hardy (1949) have shown that the duration of inspiration (T_i) is usually rather less than half the respiratory period (T) it is evident that the flow of fresh gas must be at least rather more than twice the minute volume of the patient.

If assumption 2 is modified to take account of the fact that the expiratory valve will not close until some finite time, T_v, after the start of inspiration, then it can be shown that equation (7) is modified to

$$F_a \geqslant (V_t - V_c)/(T_i + T' - T_v/2) \ldots . (9)$$

As in system A, however, this represents only a very small change in the criterion, since T_v will be only about one-tenth of T.

It is more difficult to determine what will happen if assumption 3 is modified to take account of the increase in pressure drop across the valve which accompanies an increase in flow through it. After the valve has just opened the pressure in the system will increase as the flow through the valve increases and consequently the volume of the bag will increase. If the pressure-flowrate characteristic of the valve has a gentle slope (that is, large flows can be passed for small increases of pressure above the opening pressure) only a small extra volume, including some expired gas, will enter the bag. Depending on the nature of the breathing pattern, some of this volume may still reside in the corrugated tube at the start of inspiration and so be rebreathed. If, however, the characteristic has a steep slope an appreciable volume would enter the bag, and to prevent this containing any "contaminated" expired gas it would be necessary to ensure that the bag reached its maximum volume early in expiration, before the expiration contained any gas which had been in contact with the alveoli of the lungs. It can be shown that this can be achieved if the valve first opens very soon after the start of expiration—in other words, if the fresh gas supplied by the machine during inspiration is almost as large as the patient's tidal volume.

Thus when account is taken of the effect of the various errors introduced by assumptions 2, 3 and 5 it seems probable that rebreathing of contaminated gas will be almost, if not quite, eliminated provided that the supply of fresh gas is at least equal to twice the patient's minute volume.

SYSTEM C

Expiratory valve, supply of fresh gases and reservoir bag, all close to face mask. (No corrugated tube.)

From figure 1 it is apparent that system C can be regarded as a limiting case of either system A or B in which the length of the corrugated tubing has been reduced to zero. The flow conditions of system A will be seriously altered when the length of the corrugated tube approaches zero since it can then no longer act as a depot in which the early part of expiration can temporarily reside, to be driven out of the expiratory valve, later in the expiratory phase, by fresh gases. In system B, however, the tubing merely forms an extension of the reservoir bag so that the conditions for the elimination of rebreathing in system C are the same as those in system B. If, however, any rebreathing does occur, the way in which the concentration of carbon dioxide builds up in the inspired air may well be different since mixing of each expiration with the gas in the bag will occur more efficiently in this system than in system B.

SYSTEM D

Supply of fresh gases close to face mask, separated by corrugated tube from reservoir bag and expiratory valve.

In this system during expiration fresh gas and expired gas will flow together, backwards along the corrugated tube, initially into the bag and later, when the bag has attained its critical volume, V_c, out through the expiratory valve. During inspiration, fresh gas will flow directly to the patient at a rate F_a, the remainder of the patient's inspiratory requirements being drawn along the corrugated tube from the bag.

The conditions in this system are clearly rather different from those in the three systems already considered. Any expired gas which enters the corrugated tube and is subsequently inspired will undoubtedly have been in contact with the alveoli of the lungs since it was derived from the last part of expiration. Thus, for the complete elimination of rebreathing, *no* gas from the previous expiration must be allowed to enter the lungs. The only condition under which gas may be drawn from the corrugated tubing during inspiration is if between the end of expiration and the beginning of inspiration there is a pause of duration, say T'', during which a volume of fresh gas, $F_a T''$, will accumulate in the right-hand end of the corrugated tube.

Then this volume, plus that supplied by the anaesthetic machine, must be not less than the tidal volume.

That is $\quad F_a T'' + F_a T_i \geqslant V_t$

or $\quad F_a \geqslant V_t/(T_i + T'') \ldots\ldots\ldots (10)$

Since T'' is rarely more than a small fraction of T, the period of the respiratory cycle, this condition is approximately the same as that given by equation (8). Here it will hold true whatever the nature of the expiratory flowrate pattern (since T'' may be put equal to O if necessary), but it may be rendered false by certain types of inspiratory flowrate patterns. If $T'' = O$ then no gas must be drawn from the corrugated tube during inspiration. If the inspiratory flowrate pattern is a perfect square wave, then the assumption made above ($F_a T_i \geqslant V_t$ when $T'' = O$) is justified, since the inspiratory flowrate will be constant and not greater than F_a during inspiration. However, if for the same tidal volume the inspiratory flowrate pattern is at all "peaky" some small volume of gas will at some stage during inspiration be drawn from the corrugated tube to be replaced by an equal volume of fresh gas from the anaesthetic machine towards the end of inspiration. If there is an appreciable expiratory pause ($T'' \neq O$) there would probably be a sufficient volume of fresh gas in the right-hand end of the corrugated tube to act as a buffer against this effect.

In this system there is no need to make assumptions 2, 3 and 5. It can be stated that rebreathing will be eliminated, providing the inspiratory flowrate pattern is not too "peaky", if the supply of fresh gas is at least equal to some value slightly greater than twice the patient's minute volume.

SYSTEM E

Supply of fresh gases close to face mask. Open length of corrugated tube. No reservoir bag or expiratory valve.

The conditions in this system are little different from those in system D except that during inspiration some fresh air may be drawn into the left-hand end of the tube and during expiration both expired gases and fresh gas from the machine will pass backwards along the corrugated tube straight out into the air. Assuming that wide bore connectors and tubing are used, the resistance of the system is very low. Therefore, the inspiratory flowrate pattern will be appreciably "peaky", but there will be an appreciable expiratory pause (Proctor and Hardy, 1949) so that the conditions for the elimination of rebreathing will be approximately the same as in system D.

Another method of eliminating rebreathing in this system is to use a very short length of corrugated tube. Suppose there is a definite pause, of duration T'', between the end of expiration and the start of inspiration. Then a volume, F_aT'', of fresh anaesthetic gases will enter the corrugated tube during this time. If the volume of the tube is no greater than this, then no rebreathing can occur (assuming that the expired gases are swept away from the end of the tube by draughts) However, if advantage is taken of this fact, the anaesthetic mixture will be diluted by fresh air unless F_a (T_1 + T'') is at least equal to V_t. That is to say, that the flow of fresh gases must be at least equal to about twice the patient's minute volume.

Thus, if there is an expiratory pause, rebreathing can be eliminated in this system by using a length of corrugated tubing whose volume is no greater than the product of the duration of the expiratory pause and the flowrate of fresh anaesthetic gases, but the anaesthetic mixture will then generally be diluted by fresh air. If it is desired to avoid this dilution as well as eliminate rebreathing, then the flowrate of fresh gases must be at least equal to twice the patient's minute volume and then the length of the corrugated tubing is of little consequence except from the point of view of resistance.

CONCLUSIONS

From these results it is apparent that system A has a marked advantage over the others from the point of view of economy of gases (assuming that it is desired to eliminate rebreathing). On the other hand, system E has a marked advantage over the others from the point of view of resistance to breathing—all the other systems involve the use of an expiratory valve which imposes an appreciable resistance to expiration, particularly when it is passing a large flow (Mapleson and Mushin, 1954) as it will be with the high flowrates of anaesthetic gases required to eliminate rebreathing in systems B, C, and D.

SUMMARY

The flow of gases in five different semi-closed anaesthetic systems is examined theoretically. The minimum flowrate of fresh anaesthetic gases required to eliminate rebreathing is determined in each case.

The results may be summarized by saying that rebreathing has probably been eliminated if the flow of fresh gases is at least equal to the patient's minute volume in system A (fig. 1) and at least equal to about twice the minute volume in systems B, C, D, and E. Rebreathing can also be eliminated in system E with a smaller flow of gas if there is an expiratory pause and if the volume of the corrugated tube is no greater than the product of the duration of this pause and the flowrate of fresh anaesthetic gases, but then the anaesthetic mixture will generally be diluted with fresh air.

ACKNOWLEDGMENTS

The author's thanks are due to Professor William W. Mushin for encouragement and to Miss June Williams for the figures

LIST OF SYMBOLS USED

f_r = volume flowrate of gases to or from the patient.
F_a = volume flowrate of fresh gases from the anaesthetic machine.
F_m = patient's minute volume.
n = number of respiratory cycles per minute.
T = duration of one complete respiratory cycle = $T_1 + T_2$.
T_1 = time from the start of one inspiration to the end of the same inspiration.
T_2 = time from the end of one inspiration to the start of the next inspiration
T_3 = duration of the period at the beginning of inspiration in which $f_r < F_a$
T_4 = time from the start of inspiration to closure of the expiratory valve (when taking account of the real valve characteristic).
T' = time from the end of inspiration to the opening of the expiratory valve.
T'' = time from the end of one expiration to the start of the next inspiration ("expiratory pause").
V_o = volume of reservoir bag when the pressure inside it is equal to the opening pressure of the expiratory valve.
V_1 = volume of reservoir bag at the end of inspiration.
V_2 = volume of reservoir bag at the beginning of inspiration (when taking account of the real valve characteristic).
V_r = volume inspired by the patient during the period T_4.
V_d = deadspace of patient plus face mask.
V_t = patient's tidal volume.

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CORRESPONDENCE

Tracheal intubation in trauma

Sir,—The article by Nolan and Parr[1] depicted in-line cervical stabilization and cricoid pressure during tracheal intubation in the trauma patient (fig. 2). In figure 2, in-line cervical stabilization is demonstrated as if it were a single-handed technique. It is accepted practice, however, to perform this manoeuvre as a double-handed technique (although we are sure this is the effect of the line drawing rather than the authors' practice). The same figure also depicted single-handed cricoid pressure. There has been some controversy in the literature regarding the practice of cricoid pressure in the trauma patient with potential cervical spine injury. Some authors have claimed that there is no difference in the view obtained of the larynx[2] whereas other assert that bimanual cricoid pressure enhances the view of the larynx.[3] There is debate on the safety and efficacy of either technique on the stability of the cervical spine during tracheal intubation.

In a recent investigation,[4] Gabbott examined movement of the cervical spine with single-handed cricoid pressure in subjects in whom the trachea was intubated, although unfortunately he did not compare it with bimanual cricoid pressure. In the discussion that follows, he makes recommendations that we would agree with in the management of the potentially unstable cervical spine during intubation. We would suggest that if a hard cervical collar (particularly the two-piece collar) has been applied before tracheal intubation, then the posterior piece provides adequate support for the back of the neck and single-handed cricoid pressure may then be applied. Indeed, to remove the collar may risk additional movement of the cervical spine.[5] If a hard collar is not in place then bimanual cricoid pressure is probably the safer practice.

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Sir,—The technique of manual in-line stabilization (MILS) is indeed a two-handed procedure. The line drawing in our article was made from a photograph published previously.[1] Unfortunately, the right forearm and hand of the person providing MILS is not visible from the direction the photograph was taken. Furthermore, the posterior half of the Philadelphia collar is barely visible in the original photograph and has been omitted from the drawing. The precise procedure has been described previously[1]: "an assistant applies manual in-line stabilisation by grasping the mastoid processes, whereupon the front of a semi-rigid collar can be removed safely". If the patient is fitted with a single piece collar it is our practice to undo it at the front (when MILS has been applied) and tuck the anterior section out of the way under the patient's right shoulder. We agree that this prevents the risk of moving the neck while attempting to remove the collar and may offer some posterior support during application of cricoid pressure.

While in theory two-handed cricoid pressure may be safer then one-handed in the presence of a potential cervical spine injury,[2 3] there is no evidence to support this. Furthermore, one-handed cricoid pressure allows the assistant to use the other hand to help the intubator. If intubation is likely to be very difficult (in the presence of severe maxillofacial injury, for example), it may be wise for a surgeon to apply cricoid pressure with his left hand; in the event of inability to intubate the trachea he is then well positioned to immediately perform a surgical cricothyroidotomy. It is likely that the precision of cricoid pressure applied is more important than whether a one- or two-handed technique is used. Vanner and colleagues have shown recently that the view at laryngoscopy may be improved if cricoid pressure is applied in an upward and backward direction.[4]

In summary, wherever possible it would seem wise to use the posterior section of a semi-rigid collar to provide support to the potentially injured cervical spine during application of cricoid pressure. We must await further data to determine if, in the absence of a collar, two-handed cricoid pressure is more beneficial than the one-handed technique.

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Calculating catecholamine extraction from plasma

Sir,—We would like to comment on the article by James and colleagues.[1] They measured flow rate and catecholamine concentrations in the inflow and outflow blood across several organs, and calculated the extraction ratio (ER) of catecholamines in each organ. They reported that the ER of norepinephrine by the porcine liver was 30 ± 11%. However, it has been established that every organ, with the exception of the brain, not only extracts catecholamines from plasma but also releases catecholamines into plasma.[2] This implies that plasma catecholamine concentration is determined by the balance between its spillover into the systemic circulation from sympathetic nerve terminals and its disposal from the circulation. Therefore, the ER values obtained by James and colleagues cannot be considered real, but only as "net" values.

To obtain a true ER by an organ, an isotope dilution method should also be performed. For example, Åneman and colleagues have combined a conventional and isotope dilution method, obtaining an ER for norepinephrine in the human liver of 86 ± 6%.[3] Although species difference should be taken into account, there is a possibility that James and colleagues have underestimated the ER values in each organ. Whatever the existing methodological problems, we agree with the hypothesis that the liver plays an important role in clearing plasma norepinephrine, especially in restricting the amount reaching the systemic circulation from the mesenteric organs.

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Sir,—We are in full agreement with the comment of Irita and Takahashi that our measurements reflet *net extraction ratio* of catecholamines and not *"true"* extraction ratio. This distinction was, in fact, referred to briefly in our article. Our interest in this study was to establish the effects of various organs on circulating plasma catecholamine concentrations in response to hepatectomy and we were therefore interested primarily in the net value. Although we are aware of the isotope studies and their importance in terms of establishing the *real* rate of removal of catecholamines by any organ, we are happy that the *net* effect which we examined was appropriate for our study. We concur with the observation by these authors of the importance of the liver in catecholamine metabolism.

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Extradural buprenorphine and breast feeding after Caesarean section

Sir,—I would like to comment on the article on extradural buprenorphine and breast feeding after Caesarean section by Hirose, Hosokawa and Tanaka.[1] In this study, the authors administered 0.25% bupivacaine 0.7 ml h^{-1} or bupivacaine and buprenorphine 12 μg ml^{-1} in the control study and groups, respectively, as a continuous infusion for 3 days. They also administered diclofenac suppositories 25 mg for additional analgesia. I am curious why the authors did not choose patient-controlled analgesia (PCA).[2]

Another intriguing point is why the patients were kept in hospital for 11 days. It seems that the authors had no concern as to the financial and psychological costs of this prolonged hospitalization.

The authors published a study with similar results in 1996 in *Anesthesia and Analgesia.*[3] Despite the fact that the authors used spinal anaesthesia in addition to continuous extradural analgesia in their previous study, the results were similar.

The amount of breast milk is dependent on factors such as quantity of glandular tissue in the breast, nutritional status of the mother and the psychological status of the mother.[4] I assume that the psychological burden on the patients hospitalized for 11 days was significant. The authors seemed to have ignored this issue.

On reviewing their references, it noteworthy that there is a lack of studies on this subject.

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Sir,—Dr Celebioglu questioned why we did not use patient-controlled analgesia (PCA) in our studies.[1,2] This was because we did not have enough PCA pumps for all of our subjects.

Dr Celebioglu also noted the prolonged hospitalization after Caesarean section in our studies,[1,2] which was the key point in obtaining our data on the total weight of breast milk. The length of hospitalization after Caesarean section was 12 or 13 days in our studies, which is longer than that reported in other countries.[3] Similarly, mean duration of hospitalization after laparoscopic and open cholecystectomy was reported as 11.4 and 35.5 days in Japan,[4] but only 1.8 and 2.8 days in Sweden.[5] In Japan, doctors and related professionals are well aware of the fact that postoperative hospital stay is relatively prolonged compared with other nations. This prolonged hospitalization is partly a result of the Japanese health care system. It may have affected breast feeding psychologically after Caesarean section, but it had no effect on between-group evaluation of our data, all of which were obtained during the same length of hospital stay.

We appreciate that Dr Celebioglu compared our two studies. Postoperative analgesia was performed with or without extradural bupivacaine in the first study,[1] and in the second study it was performed with extradural bupivacaine or extradural bupivacaine plus buprenorphine.[2] After we reported that extradural bupivacaine after Caesarean section improved breast feeding,[1] many clinical researchers asked us about the effect of extradural opioids on breast feeding. The second study was designed to evaluate the effect of extradural buprenorphine on breast feeding after Caesarean section. Taken together, breast feeding with postoperative extradural bupivacaine and buprenorphine was suppressed to the same level as that without extradural analgesia after Caesarean section.

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Why the Y?

Sir,—Perhaps it is a sign of secular times but, in searching for the essential J. Y. Simpson, and putting a modern "spin" on his life, Rae and Wildsmith[1] have missed the importance of religious faith to the era, the environs and his life.[2] It was a life lived during one of turmoil in Scotland's theological history. The defence of anaesthesia, on biblical textural grounds, is all the more poignant for the fact that Simpson was active in the disruption of the Church of Scotland in 1843 and is identified with the more radical, and fundamental break-away, Free Church.[2,3] It may sound pious nowadays, but Simpson's own analysis of his worth was that his greatest discovery, in a lifetime of them, was that "I have a Saviour".[4]

The acquisition of the sobriquet,[1] "Young", intrigued a generation of assiduous anaesthesia historians. Armstrong Davison stated that "... and the story how and why he assumed his second name, "Young", indicates his forceful and tactless behaviour".[5] W. S. Sykes devoted much of a chapter to the rumour, confirming that the whispers of the adoption of a middle name, with which Simpson had not been baptized, were true.[6] Sykes concluded it was an affectation adopted, when at the age of 28 yr and very conscious of his youth, Simpson had the temerity to apply for the Chair of Midwifery in Edinburgh. It is a mystery as to why it ever became an issue and subject of rumour that Armstrong Davison's readers would have known all about.[5] Armstrong Davison's "story" has gone to his grave. Or has it?

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Sir,—We thank Dr Conacher for his interest in, and comments on, our editorial. It was produced to indicate why the sesquicentenary celebration in Edinburgh was used to mark Simpson's "whole contribution to medicine" rather than just the anniversary of the first anaesthetic use of chloroform. We did refer to Simpson's "extensive knowledge of the bible" where it was relevant, but deliberately eschewed considering his involvement in the religious controversies of the day; these were not immediately relevant to our theme. In addition, we do appreciate that an *incorrect* reference to such controversy might have produced even more vigorous comment than Dr Conacher's.

The source of the sobriquet "Young" seems self-evident to us. He was the youngest of nine children, born 4 yr after his immediate senior–surely he was neither the first nor the last such child to be nicknamed "Young". The really intriguing aspect is why Armstrong Davison and Sykes were so obsessed with the issue. Both used it to denigrate Simpson, but neither provided any primary source information–very uncharacteristic behaviour for such "assiduous historians". Thus we too would like an answer to Dr Conacher's final question, but we wonder if it is simply the historical equivalent of the "tall poppy" syndrome, precipitated by their clear opinion that Simpson had not been as assiduous as he might in deflecting the credit he was often given for "discovering" anaesthesia.

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Propofol in paediatric intensive care: further evaluation is justified

Sir,—We were interested to read the study by Martin, Murthy and Petros[1] suggesting that infusion of propofol may be used safely to sedate critically ill children after cardiac surgery, and support the recommendation by Hatch that larger controlled studies need to be undertaken to develop criteria for its safe use.[2] The ICU at Frenchay hospital admits 60–80 children per annum, mainly after head injury or with other neurosurgical/neurological diagnoses. We believe that continuous infusion of propofol offers advantages in sedating these children, as it allows rapid changes in the level of sedation, facilitating rapid and repeated assessment of the child's level of consciousness and neurological function.

We audited our experience with the use of propofol infusions to sedate children over a 3-yr period.[3] Propofol was infused alone or in combination with an opioid. The maximum infusion rate of propofol allowed was 6 mg kg^{-1} h^{-1}. If this failed to achieve adequate sedation, propofol was discontinued and midazolam was used. No child received propofol if there was evidence of respiratory tract infection, and the infusion was discontinued if the child developed lipaemic serum. There were 158 children admitted, 71 of whom received propofol for sedation, usually in combination with an infusion of morphine (74.6% of children). Median age was 9.5 yr (range 10 months to 15 yr). All children were admitted after head injury or with another neurosurgical/neurological diagnosis, except for three children who were admitted with severe burns.

Median rate of infusion of propofol was 3.1 (range 0.6–6.0) mg kg^{-1} h^{-1} for a median duration of 16 (range 2–149) h. All children were adequately sedated except for two in whom midazolam was substituted for propofol when 6 mg kg^{-1} h^{-1} failed to sedate the child adequately. All children were easy to assess neurologically by simply reducing the rate of infusion of propofol. Median time to extubation after stopping the propofol infusion was 40 (range 10–510) min. No child developed lipaemic serum, unexplained acidosis, hepatic or cardiac failure.

The dose of propofol used was slightly more than the median rate of infusion of 2.1 mg kg^{-1} h^{-1} reported by Martin, Murthy and Petros.[1] This probably reflects the deeper level of sedation required in the management of patients with head injuries or other diseases likely to cause increased intracranial pressure. In every other aspect our experiences were similar. We support the conclusion of Martin, Murthy and Petros that propofol may be used safely to sedate children receiving intensive care provided that the maximum infusion rate is not exceeded. The criteria they recommend for the safe use of propofol in children should be used as the basis of further larger studies evaluating the use of the drug to sedate other groups of critically ill children in addition to the postoperative cardiac surgical population.

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Sir,—We welcome the comments of Young and Manara. Propofol continues to be used in the PICU throughout the UK and we are pleased to read that its sensible use has produced no problems. We are in the process of setting up a prospective study on the use of propofol in the PICU and the incidence of propofol associated metabolic acidosis, and would welcome collaboration with other centres.

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Sevoflurane in acute airway obstruction

Sir,—I was interested to read Mostafa and Atherton's report on the use of sevoflurane in patients with difficult airways.[1] They remarked how rapidly deep anaesthesia was achieved, although none of their patients had significant respiratory obstruction.

I recently anaesthetized a 75-yr-old woman with stridor caused by laryngeal carcinoma. She was obese and a heavy smoker. She had refused any procedure under local anaesthesia. After administration of nebulized epinephrine, anaesthesia was induced with sevoflurane in 100% oxygen. Starting at a concentration of 2%, this was increased in increments to 8%. Loss of consciousness was rapid (less than 1 min). After 2 min, I attempted laryngoscopy, but the patient gagged. A similar incident occurred at 5 min. In the meantime, her airway was becoming increasingly difficult to hold owing to loss of muscle tone in a bulky neck. Finally, after 10 min, laryngoscopy was possible; the vocal cords could be seen and succinylcholine was given. Intubation, however, was unsuccessful and necessitated intervention of the ENT surgeon with a rigid laryngoscope. The improved view allowed intubation with a size 6 tracheal tube.

Deep anaesthesia with sevoflurane was hard to achieve in this situation. It was better than with halothane. Sevoflurane has a lower blood:gas solubility, but is much less potent than halothane. In the case of respiratory obstruction, is potency as important as solubility?

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1. Mostafa SM, Atherton AMJ. Sevoflurane for difficult tracheal intubation. *British Journal of Anaesthesia* 1997; 79: 392–393.

Sir,—I was interested to read about the three patients with expected difficult intubation in whom inhalation induction with sevoflurane proved useful in airway management.[1] Since the introduction of sevoflurane in Singapore, I have found this agent to be similarly useful in patients with head and neck tumours presenting for examination under anaesthesia, biopsy or for surgery. Two cases may be worth mentioning.

An obese 56-yr-old woman presented with a massive multinodular goitre for thyroidectomy. Awake fibreoptic intubation proved impossible because the patient became distressed, uncooperative and hypoxic during the attempt. After inhalation induction with sevoflurane up to 6% in 100% oxygen, direct laryngoscopy was undertaken to reveal a grade 4 larynx.[2] Blind passage of a gum elastic bougie into the trachea was suggested by the patient's cough and confirmed by capnography when a tracheal tube was successfully "railroaded".

A 48-yr old man presented with a nasopharyngeal tumour for examination under anaesthesia and biopsy. After inhalation induction of anaesthesia with sevoflurane in oxygen, direct laryngoscopy was performed. A haemorrhagic tumour was found occluding the laryngeal inlet. Intubation was not attempted and spontaneous ventilation was maintained using sevoflurane in oxygen while the surgeon proceeded to perform a tracheostomy.

I agree with Mostafa and Atherton that sevoflurane has replaced halothane for inhalation induction of anaesthesia in the management of the difficult airway. I have found no advantages in the use of nitrous oxide in this particular situation.

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1. Mostafa SM, Atherton AMJ. Sevoflurane for difficult tracheal intubation. *British Journal of Anaesthesia* 1997; 79: 392–393.
2. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; 39: 1105–1111.

Sir,—Thank you for the opportunity to reply to the letters of Dr Board and Dr Ip-Yam. Our interest in using sevoflurane in the management of patients with difficult airways was not how *rapidly* it achieved anaesthesia, albeit important, as much as how *easily* anaesthesia was accomplished and how the airway was maintained without difficulty. It is pertinent to state that our experience is not limited to the three cases we described. Our impression is supported by Dr Ip-Yam's letter describing the use of sevoflurane in the management of children and adults with difficult airways. Our experience is also corroborated by the recent report of Frerk and Tordoff[1] in which they described the management of three patients with difficult airways. Furthermore, and perhaps most important, the low blood:gas solubility of sevoflurane implies that, if difficulty is encountered with induction, it should be easier and quicker to lighten anaesthesia and wake the patient. This is the great advantage of inhalation induction.

Dr Board unfortunately raises the wrong question. In certain cases of stridor, such as in the patient he described, the choice for securing the airway should lie between awake intubation and tracheostomy under local anaesthesia, *not* the potency or solubility of a general anaesthetic agent. In our view, such a patient should not be anaesthetized before securing the airway. General anaesthesia may reduce muscle tone which can lead to complete airway obstruction. But sometimes our approach is not feasible because of lack of cooperation of the patient, or because of lack of an anaesthetist skilled in awake intubation.[1] In addition, the use of halothane may be contraindicated, as in the cases we described. In these circumstances the use of sevoflurane for inhalation induction may offer the safest solution. As Dr Board had not used halothane when he encountered difficulties it would be impossible for anyone to judge if it or sevoflurane was the better agent.

In conclusion, we would maintain that inhalation induction with sevoflurane is a useful technique in the armamentarium of anaesthetists for the management of patients with difficult airways.

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1. Frerk CM, Tordoff SG. Sevoflurane and the difficult airway: A report of three cases. *Today's Anaesthetist* 1997; 12: 121–122.

Anaesthesia for surgery of emphysema

Sir,—Dr Conacher's comprehensive review article on anaesthesia for surgery for emphysema[1] is marred by the advocation of extradural analgesia as the only vital analgesic technique.

Paravertebral analgesia blocks not only the intercostal nerves but also the sympathetic chain and posterior primary rami, providing equally effective postoperative analgesia in addition to inhibiting the stress response to surgery.[2] It has fewer side effects than extradural analgesia,[2,3] and is safer and technically easier to perform.[4] By producing only unilateral block, paravertebral analgesia avoids hypotension and thus the need to administer excessive i.v. fluids or vasopressors to maintain tissue perfusion.[3]

Balanced analgesia, by blocking both peripheral and central pain mechanisms, has also been recommended in the form of preincisional paravertebral block, opioid premedication, preoperative non-steroidal anti-inflammatory drugs and postoperative continuous paravertebral block.[2] It provides effective postoperative analgesia and minimizes the loss in pulmonary function seen after thoracotomy.[2]

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1. Conacher ID. Anaesthesia for the surgery of emphysema. *British Journal of Anaesthesia* 1997; 79: 530–538.
2. Richardson J, Sabanathan S, Mearns AJ, Evans CS, Bembridge J, Fairbrass M. Efficacy of pre-emptive analgesia and continuous extrapleural intercostal nerve block on post-thoracotomy pain and pulmonary mechanics. *Journal of Cardiovascular Surgery* 1994; 35: 219–229.
3. Matthews PJ, Govenden V. Comparison of continuous paravertebral and extradural infusions of bupivacaine for pain relief after thoracotomy. *British Journal of Anaesthesia* 1989; 62: 204–205.
4. Berrisford RG, Sabanathan S. Direct access to the paravertebral space at thoracotomy. *Annals of Thoracic Surgery* 1990; 49: 854.

Sir,—I would agree with Dr Lafrenière that paravertebral block, balanced with opioids and non-steroidal anti-inflammatory drugs (NSAID), is one of several options for analgesia that could be justified, on the grounds suggested, for patients whose pulmonary condition renders them suitable for routine thoracotomy or thoracoscopy. However, for patients with bilateral emphysematous conditions, verging on respiratory failure, undergoing lung transplantation, volume reduction surgery or non-thoracic surgery, the technique does not have a track record and would not be viewed as best practice.

For the last group of patients (those most likely to be encountered by the non-specialist in the middle of the night) the risk of pneumothorax[1] in a vulnerable population would have to be added to the dangers caused by the balancing of analgesia with NSAID. The use of non-essential drugs that can precipitate renal failure in the presence of low volume urine production are viewed askance by those caring for patients in whom one organ is already failing. These patients may require toxic immunosuppressants, and a vital element in their recovery is fluid restriction. The international consensus, from the review I undertook, is that extradural analgesia is the gold standard and I would not, at this time in the evolution of the third age of thoracic anaesthesia,[2] suggest anything less except in failure to achieve that standard. In which case, there are safer options than paravertebral block and NSAID.

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1. Lonnqvist PA, Mackenzie J, Soni AK, Conacher ID. Paravertebral blockade–failure rate and complications. *Anaesthesia* 1995; 50: 813–815.
2. Conacher ID. Anaesthesia for the surgery of emphysema. *British Journal of Anaesthesia* 1997; 79: 530–538.

Suboptimal use of inhaled aerosol therapy during mechanical ventilation in intensive therapy units in the UK and Ireland

Sir,—Aerosol delivery of nebulized drugs appears less efficient than in patients breathing spontaneously and is highly dependent on the method used.[1,2] To examine the pattern of use of aerosol drug therapy during mechanical ventilation in intensive care units in the UK and Republic of Ireland, and to establish how frequently proven methods of optimizing drug delivery were used, a postal questionnaire was sent to consultants in those intensive care or high dependency units listed in the 1995 Directory of Emergency and Special Care Units in the UK and Ireland, between March and October 1995. In the event of no response, after 3 months a reminder letter was sent. The questionnaire enquired about the size and type of the intensive care unit and number of patients treated. Details were sought about the use of aerosol therapy during mechanical ventilation, including drugs, ventilators and methods of nebulization used.

Responses were received from 175 of 213 (82%) units. All had used aerosol drug therapy during mechanical ventilation within the last year and 168 units had used it within the previous month. Drugs used in the previous month included beta$_2$ adrenoceptor agonists (168 units), anticholinergic drugs (140 units), corticosteroids (57 units), antibiotic or antiviral agents (18 units), prostacyclin (13 units) and surfactants (three units). Most (162) units used jet nebulizers, while the simpler, less expensive and possibly more efficient[1] metered dose inhalers were used less often (34 units). Although very efficient,[3] ucspasonic nebulizers were used rarely (six units).

Table 1 Numbers (%) of units using methods which enhance aerosol delivery during mechanical ventilation. *In units who administered these drugs within the past year

Method of improving delivery	Users (% responders)	Non-users	No response
Jet nebulizers (162 units)			
Placement on inspiratory limb of ventilator system	43 (27%)	115	4
Placement 10–30 cm from Y-piece on inspiratory limb	8 (5%)	150	4
Use of spacer	5 (3%)	157	0
Use of ⩾5 ml nebulizer solution	66 (43%)	89	7
Use of inspiratory phased jet nebulization	67 (41%)	95	0
Interruption of humidification	31 (22%)	109	22
Adjustment of ventilatior settings	46 (29%)	114	2
Nebulizer apparatus removed between use	153 (94%)	9	0
Metered dose inhalers (34 units)			
Use for administering beta$_2$ agonists*	27 (79%)	7	0
Use for administeing anticholinergic drugs*	20 (59%)	14	0
Use for administering corticosteroids*	20 (38%)	14	0
Placement on inspiratory limb of ventilator system	13 (38%)	21	0
Placement 10–30 cm from Y-piece on inspiratory limb	2 (6%)	32	0
Use of spacer	7 (21%)	27	0
Interruption of humidification	6 (21%)	22	6

Methods of enhancing aerosol delivery were used infrequently (table 1). Most units did not position the nebulizer on the inspiratory limb of the breathing system and few used spacers, even though combining these methods may double aerosol delivery to the patient.[1,4] Less than 50% of the responding units used a high drug solution volume in jet or ucspasonic nebulizers, even though delivery may be doubled by increasing the volume of the nebulizer solution from 3 to 6 ml.[5] Most units did not adjust ventilator settings during nebulization and may thus have inadvertently altered the conditions of ventilation, including respiratory minute volume.[1] Discontinuing humidification during aerosol administration improves delivery[2] but was performed infrequently. Most units removed nebulizer apparatus from the breathing system when not in use, which is good practice as it reduces the risk of bacterial contamination.[1]

In spite of the drawbacks in using a postal survey to study the management of patients, we believe the results are a valid reflection of recent practice in the UK and Ireland as the response rate was high. It showed that aerosol drug therapy is used often during mechanical ventilation but the methods used are suboptimal and could easily be improved by some simple modifications. The British Thoracic Society has recently issued guidelines on nebulizer use during mechanical ventilation.[6] Adoption of these guidelines will improve aerosol drug delivery to patients undergoing ventilation in intensive care units, and this is expected to improve the effectiveness of drugs administered by this route.

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1. O'Doherty MJ, Thomas SHL. Nebuliser therapy in the intensive care unit. *Thorax* 1997; 52 (Suppl. 2): S56–59.
2. Dhand R, Tobin MJ. Inhaled bronchodilator therapy in mechanically ventilated patients. *American Journal of Respiratory Critical Care Medicine* 1997; 156: 3–10.
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BOOK REVIEWS

Critical Care Management. Case Studies: Tricks and Traps. G. R. PARK AND M. R. PINSKY (editors). Published by WB Saunders, London. Pp. 303; indexed; illustrated. Price £29.95.

This book is a collection of 51 case reports covering 11 different areas of critical care, including organ failure, obstetric critical care, drug interactions and sepsis. The reports are written by 35 experts from the UK, USA and Australia.

All of the case reports have the same format. A case is described where some aspect of the care has been less than optimal because the physicians involved have fallen into a "trap", which the editors describe as a situation where a logical plan of diagnosis and treatment was applied, but was inappropriate in the particular circumstances described. Various "tricks" are then described, clinical signs, tests and manoeuvres, which would have helped to avoid the "trap". A brief paragraph on follow-up and a few key references complete the report.

This format makes the book very interesting to read. Knowing there is some aspect of the care provided that is less than perfect in each case, you read the report trying to spot the trap, and making comparisons with your own practice and what you would do in the same circumstance. The traps range from the very obvious to some fairly subtle points, and cover a wide range of critical care problems. The tricks sections are in effect discussions of the cases, and these are generally well written and focused.

In America there are far more critical care beds available, and therefore physicians are able to admit less severely ill patients than in the UK. This is apparent in the cases selected for this book; several of the patients described would not be seen commonly in an intensive care unit in the UK, and would be managed on the ward or coronary care unit. This gives the book a broader scope than is apparent from the title, as it covers both critical care and acute medicine. Transatlantic differences in patient management are also apparent, in particular with respect to the use of pulmonary artery catheters. As this is a book of case reports, the wide range of conditions and treatments resulting from the multinational authorship add greatly to the interest of the book.

The book has an international authorship and distribution, and the editors have been careful to ensure laboratory and other data are given in both SI and non-SI units. A comprehensive list of abbreviations and normal laboratory values is included in an appendix.

My only criticism of the book concerns the section on increased intrathoracic pressure where the theme of auto-PEEP occurs many times. Otherwise there is little overlap between the cases described.

This is definitely a book that should be read, rather than a reference book. Although it will be of great interest to the trainee, even seasoned intensivists will glean many useful nuggets of information. I would recommend it to all physicians involved in intensive care.

J. D. Young

Anaesthesia Review–13. L. KAUFMAN AND R. GINSBURG (editors). Published by Churchill Livingstone, Edinburgh. Pp. 330; indexed; illustrated. Price £32.50.

This is the latest in a long and well known series of reviews by the same editors; 27 contributors opine in 17 chapters, with Dr Kaufman penning three of these. The origin of these contributors suggests a sad view of British anaesthesia–no anaesthetist living north of a line drawn between Southampton and Cambridge has contributed to this book. With such a large number of authors, consistency of style is difficult to achieve. The chapters vary in both style and readability from the exceptional to the abysmal.

The relevance of the brief review of the first ether anaesthetic given at University College Hospital is not obvious. It is a well worn story, albeit well told, but reprinted from an earlier edition in the series and singularly out of place in a review of modern medical practice relevant to anaesthesia–151 yr on.

Dr Kaufman introduces the real "meat" of the book with "medicine relevant to anaesthesia", with 138 references providing support for his contribution. "Cocaine" merits three sentences in the section on the cardiovascular system but avoids any reference to typical therapeutic doses to compare against the tacit reference to illicit abuse–not helpful when the latter is better covered specifically later in the book.' Similarly, under a complete section on "sickle cell", although reference is made to a review of sickle cell crisis elsewhere, the six sentences in this section would not help in anaesthetizing a sufferer of the disease. Under the "miscellaneous" heading, a puzzling sub-section entitled "antiemetics" refers to work on the effect of ranitidine and omeprazole on gastric emptying, but omits to mention emesis *per se*.

The chapter on "renal physiology" was much more concise and obviously useful; of the 45 references, several were from 1995. Physicians (hepatologists?) from Birmingham provided a comprehensive update of the "virology of hepatitis", which is well worth reading even if only to emphasize the need to avoid complacency when dealing with body fluids. A particularly useful feature here is the "key points", something which reappears inconsistently throughout the book.

Thyroid storm is covered well in the next chapter on "thyroid disorders" (one has always been wary of this). Perhaps, though, a comparison with the diagnosis of malignant hyperpyrexia (MH) would have been helpful when MH may occur in a typical district hospital only once in 10 yr, with thyroid storm even less frequently. There was surprise that more than 20 yr after the adoption of the Systeme International, there was reference to milligrams of calcium in serum (on page 79), incomprehensible to many in the UK.

In the preface, the editors extol the importance of an understanding of "ion channel receptors" in the modern practice of anaesthesia. Unfortunately, comprehension was not aided by Dr Gibb's erudite discourse on the subject. While this may be a learned treatise, it did nothing to enlighten with its use of unfamiliar terms and unexpanded abbreviations. What are metabotropic receptors? AMPA receptors? and is $GABA_A$ anything to do with GABA or gamma amino butyric acid? Hiding in this jungle of a chapter is, however, a superb piece on neuromuscular transmission

"Intravascular monitoring" provided a rare view on both the history and developments in the pipeline, but "euthanized"' sheep were an unnecessary abuse of English!! Chapters on the "laryngeal mask airway" and "cardiopulmonary resuscitation" were well presented and salient, the former ending with the "key points", while the latter a section of "conclusion". Drs Matta and Menon from Cambridge provide two chapters on "management of acute head injury" with "key points" for the idle! The 38 pages are well used. However, each chapter had its own list of references, 14 being duplicated (one list of references, in correct order (Martin before Matta and Marx) would have been more efficient).

"Parenteral nutrition" is well covered and followed appropriately by a chapter on "extravasation" of parenteral nutrition fluid and other drugs. A whole chapter devoted to a common occurrence among anaesthetist practitioners was apposite. The list of (relatively) safe drugs to extravasate was also useful.

"Substance abuse" provides a parents' as well as practitioners' walk through the life and death associated with "cutting", "bodypacking", "Ecstasy", "Adam", and "Eve" and much more. Essential reading for those in contact with teenagers and their culture. Again, following on from one cause of psychiatric disturbance comes a well placed chapter on the "pharmacology of psychiatric illness". Here the reversible inhibitors of monoamine oxidise A (RIMA) and selective serotonin inhibitors (SSRI) are placed in context, especially in respect of anaesthesia, practitioners of which took a long time to come to terms with the original MAOI class of drugs.

The book finishes with two (two?) updates, both from Dr Kaufman. These are easy to read and well chosen.

In summary we have something of a "curate's egg" of a book. There is no doubt that the good parts outweigh the bad. Despite all the caveats, I commend it strongly as a good value addition to the bookshelf of both the individual and departmental libraries.

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"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL I

Diaphragmatic dysfunction: an outmoded concept

The expression "diaphragmatic dysfunction" is a mellifluous phrase used when considering the respiratory changes associated with major surgery.[1–5] A recent editorial in this journal concerning the effects of laparoscopic cholecystectomy[6] discussed inhibition of diaphragm function, modified breathing patterns and changes in the abdominal contribution to breathing attributed to reflex diaphragmatic inhibition: all of these concepts have been considered to represent diaphragmatic dysfunction. However, some articles have voiced muted doubts about the concept,[7–9] which I believe is now sufficiently threadbare to require that the expression be used rarely, if at all, when we consider changes in respiratory pattern after abdominal surgery.

The expression was first used by Ford and co-workers in an article entitled "Diaphragm function after upper abdominal surgery in humans".[10] They applied the theory that diaphragm contraction and descent during inspiration not only generates a decrease in pleural pressure (Ppl), but also an increase in abdominal pressure (Pab). In contrast, if an inspiration is generated by the intercostal muscles acting alone, abdominal pressure decreases. This decrease is the same as the decrease in pleural pressure because the diaphragm is inactive and does not establish a pressure difference between the pleural and abdominal cavities. The relative changes in Pab and Ppl should indicate the relative contributions of these inspiratory muscle groups, the diaphragm and ribcage muscles to inspiratory activity.[11] If Pab changed less, relative to the change in pleural pressure during inspiration, then a "dysfunction" of the diaphragm was present. This analysis is confounded when the abdominal muscles are active. Abdominal muscle contraction followed by relaxation can generate relative changes in Pab and Ppl very similar to intercostal activity (fig. 1). The effect of abdominal muscle activity was generally discounted by early investigators.

Studies employing this analysis have used different means of expressing the relative changes in Pab, Ppl and trans-diaphragmatic pressure (Pdi), which is calculated from the two preceding values, thus: $P\text{di} = P\text{ab} - P\text{pl}$.

The most frequent expressions used are Pab/Ppl (which is awkward because the denominator has a negative value) and Pab/Pdi (which is mathematically related, being $1/(1 - P\text{pl}/P\text{ab})$). Most studies reported that the pressure swings were measured from "maximum to minimum" values, irrespective of time, within a respiratory cycle, read from a chart recorder.[10 12–15] However, it is evident from the theory outlined that to provide an accurate indication of muscle contribution to inspiration, the pressure changes compared must be *during the same period of inspiration.* If the measurements include abdominal pressure changes during expiration, caused by abdominal muscle contraction, this affects the "maximum to minimum" estimates.

Ford and co-workers suggested that the changes they reported "may be attributable to diaphragm dysfunction".[10] Further studies followed, with one using the term "diaphragmatic dysfunction" in the title.[14] Such studies also used other indirect measures of diaphragm function, such as the relative motion of the ribcage and abdomen.[16] Ford and co-workers have since reviewed the topic[7] and are now more circumspect with the term "dysfunction", preferring to describe a change from diaphragm to intercostal activity in a review of the extensive animal studies which support reflex inhibition via visceral afferent pathways.

Unfortunately, the term "diaphragmatic dysfunction" is used when other plausible possibilities have been present. These included phasic activity of the abdominal muscles, which can cause abdominal pressure changes in addition to those changes generated by the diaphragm, and also causes of increased ribcage muscle activation.

Abdominal muscle activity

The normal pattern of change in Pab is an increase during inspiration, with a decline during expiration. However, the abdominal muscles often become active in expiration, for example: in exercise; with impedance to inspiration[17]; in patients with obstructive airways disease[18]; and during anaesthesia.[19] Abdominal muscles are also active in patients after surgery: their activity causes an additional phase of increasing abdominal pressure during expiration. This pressure subsides rapidly at the onset of the next inspiration. It can be greater than the pressure change in inspiration, so that the usual increase in pressure associated with inspiration and contraction of the diaphragm can be swamped by a much greater pressure swing induced by abdominal muscle contraction.[20] In the awake subject, this activity may be continuous, but during sleep or airway obstruction, phasic activity during expiration is more common. Early direct observations of abdominal muscle activity after surgery were later supported by studies which showed activity in patients after thoracotomy,[21] cardiac surgery,[8] abdominal surgery[9] and transiently after laparoscopic surgery.[22]

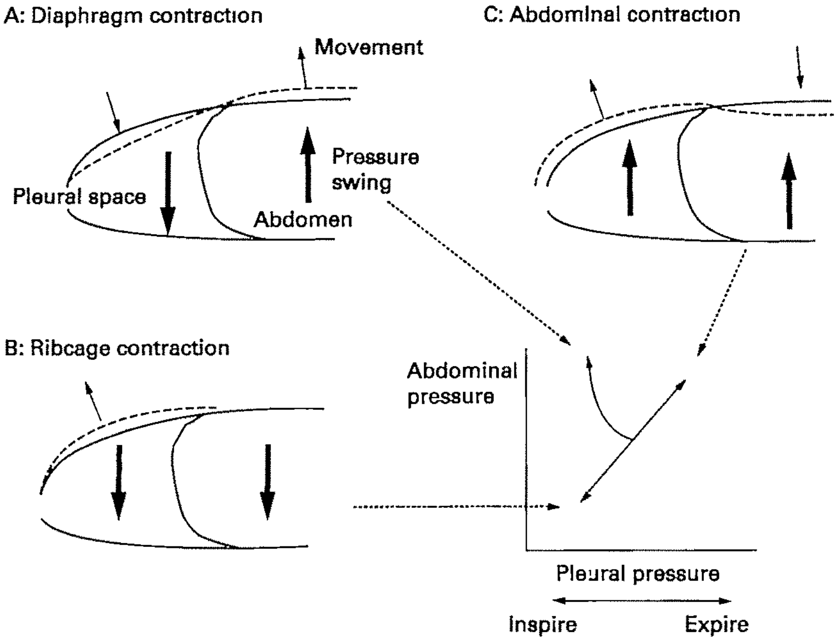

Figure 1 Schematic representation of the actions of respiratory muscle groups. A: Diaphragm contraction: the diaphragm descends, displacing the abdominal wall outwards. Pleural pressure decreases and the ribcage is pulled inwards by the increased pressure difference. B: Ribcage contraction: the ribcage is displaced outwards and pleural pressure decreases. The inactive diaphragm does not create a pressure difference and the abdominal pressure decreases in parallel with pleural pressure. C: Abdominal contraction: the abdominal wall moves in, increasing abdominal pressure and forcing the abdominal contents and the diaphragm cranially. Pleural pressure increases and lung volume decreases (expiration). Relaxation of the abdominal wall reverses these changes.

A plot of abdominal pressure and volume can show how the abdominal muscles are working.[9 22] When abdominal pressure increases as a result of diaphragm action, the abdominal wall moves out: if the increase in pressure has been caused by abdominal muscle contraction, the abdominal wall either does not move (but may change its shape) or moves inwards if the diaphragm does not resist being forced upwards into the ribcage.

Activation of ribcage muscles

The ratio of changes in abdominal and pleural pressure during inspiration reflects the degree of activation of the ribcage and diaphragm. After operation, the predominant effect may be an increase in ribcage muscle action. An increase in the proportion of drive to the ribcage muscles can result for several reasons. If there is an overall increase in drive, such as is common after surgery, then the proportional activation of other inspiratory muscles is likely to increase to a greater extent than that of the diaphragm.[23] Even if overall drive does not increase, changes in airway resistance with sedation can lead to marked increases in ribcage movement,[24] probably from a reflex increase in activity of the ribcage muscles, which are richly supplied with muscle spindles. Nimmo and Drummond found that patterns of pressure changes, consistent with increases in ribcage activity, were significantly related to airway obstruction.[9] Clergue and colleagues[8] concluded that increased ribcage muscle activity and phasic expiratory activity were responsible for the postoperative changes they described, with no convincing evidence of alterations in diaphragm activity. Finally, even with the same drive and relative intercostal activity, abdominal pressure changes are greater, and abdominal movements less, if abdominal compliance is decreased, for example by tonic abdominal activity.[25]

How can dysfunction of the diaphragm be defined and recognized? A simple definition is that a muscle is functioning less well if it fails to generate its normal tension for a given degree of electrical activation. In patients after abdominal surgery, this is not easy to demonstrate. Respiratory frequency increases and tidal volume is reduced after abdominal surgery.[26] Consequently progressive activation of the diaphragm during inspiration is cut short more quickly, and the degree of activation at the end of inspiration is less than that before operation. Simple measures of activity at the end of inspiration are thus of no value in determining changes in diaphragm properties. Changes in electrical activity, such as those reported after extradural block in postoperative patients,[27] could be attributed to changes in respiratory frequency that occur at the same time. When electrical activity was related to transdiaphragmatic pressure, extradural analgesia did not alter the relationship between electrical activity and pressure generated by the diaphragm, despite changes in other "indices of contractility" such as $\Delta Pab/\Delta Pdi$.

In five patients after abdominal surgery, direct maximal stimulation of the phrenic nerves, with measurement of the resultant diaphragmatic pressure, was used to assess any changes in diaphragm contractility. Although this study would have been technically difficult, the results suggested that there was no change in contractility.[13]

The remaining attribute of the concept of "diaphragmatic dysfunction" is of central inhibition of inspiration, caused by visceral pain. Limitation of vital capacity has long been recognized to accompany abdominal surgery, and to be more marked the closer the incision is to the diaphragm. More recently, laparoscopic intra-abdominal procedures have also been recognized to limit maximal inspiration, and this effect is more severe after cholecystectomy than lower abdominal procedures, suggesting that visceral damage is important.[28] The exact neural pathways involved are not clear: extradural anaesthesia can only partly restore vital capacity, and the activity of the diaphragm on maximal voluntary inspiration is more suppressed than "semi-voluntary" maximal manoeuvres such as sniff.[28] There are no data to indicate that inhibition of maximal inspiration is exclusive to the diaphragm.

The concept of "dysfunction" led to interventions to reduce it. Two approaches were investigated. Aminophylline, which can improve muscle contractility in some circumstances, was given to patients after upper abdominal surgery.[15] The example trace in this study shows that considerable abdominal muscle activity was present, with abdominal pressure increasing during expiration and suddenly decreasing at the start of inspiration. Aminophylline abolished this abdominal muscle action, converting the trace to one that resembled the preoperative pattern. Nevertheless, the authors rejected the possibility that abdominal muscle action was responsible for the changes they reported, on the grounds that the pressure swings were similar before and after operation, and suggested that administration of aminophylline improved the index $\Delta Pab/\Delta Pdi$ and thus improved diaphragm function. However, in experimental animals treated with aminophylline, direct measurements of diaphragm length did not show an improvement in diaphragm contractility,[29] and another clinical study found an increase in maximal inspiratory effort that was probably a centrally mediated effect.[2] It appears that aminophylline acts as an analeptic. Even if it were an effective therapy, it is unlikely to prove popular: it has a narrow therapeutic margin, several adverse effects and important interactions with other treatments used in postoperative patients.[30]

If diaphragm dysfunction is caused by reflex inhibition, then extradural block might interfere with the reflex and improve mechanics. Motor block of the abdominal muscles also has a potentially important effect on chest wall movement. Mankikian and co-workers studied the effects of thoracic extradural block to T4 obtained with 0.5% bupivacaine, using $\Delta Pab/\Delta Ppl$ and chest wall measurements.[12] No electrical measurements of abdominal muscle activity were made, but activity was clinically evident in two of the 12 patients. The change in abdominal pressure was measured as "peak inspiratory minus peak expiratory pressure" so the expiratory pressure included contributions from abdominal muscles. Not surprisingly, the main effect of what was probably a large degree of abdominal motor block was a small increase in the abdominal pressure swing, and an increase in abdominal outward movement on inspiration. They concluded that diaphragm function had improved, although the probable abdominal muscle motor block makes this conclusion uncertain. A subsequent study from these workers[27] recognized the problems of expiratory abdominal muscle action and incorporated changes in the measurements of the pressure swings to avoid the expiratory phase. They also measured diaphragm electrical activity and found no evident changes in contractility. Despite paradoxical breathing patterns, where the abdomen moved inwards during inspiration, the electrical activity of the diaphragm persisted. They concluded that the diaphragm was inhibited by visceral pain and that extradural block removed the afferent stimulus causing this inhibition. In fact, the most prominent effects noted were a decrease in respiratory rate, an increase in tidal volume and a greater outward movement of the abdomen, all of which could result from abdominal sensory and motor block.

More invasive studies did not reveal important changes in diaphragm function. Fratacci and colleagues[21] studied the effects of thoracic extradural block in a small number of patients after thoracotomy, in whom sonomicrometre crystals had been implanted to measure changes in diaphragm length. Extradural analgesia did not improve contraction: indeed, paradoxical lengthening occurred in three patients. The authors suggested that the ribcage muscles were contracting more strongly. However, a representative trace obtained before extradural block revealed an increase in gastric pressure towards the end of expiration. This pressure would act to lengthen the inactive fibres of the diaphragm in expiration, which would subsequently tend to shorten when the abdominal muscles relaxed at the onset of inspiration. Thus an alternative explanation for the paradoxical effect of extradural anaesthesia would be abolition of the lengthening in expiration, and hence less "shortening" action during inspiration. A general criticism that can be levelled at many of these studies of postoperative patients is that they were made over only short time periods, and may not have been entirely representative. Longer recordings show frequent changes in respiratory pattern, with abnormalities developing and disappearing, sometimes quite quickly. Abnormal breathing patterns are significantly related to airway obstruction.[9]

Considering the complex interactions of the respiratory muscles, to expect that the action of the diaphragm could be analysed and assessed with a single simple measurement was unrealistic. The uncritical application of the concepts of abdominal and pleural pressure change associated with diaphragm action, in clinical circumstances where the other respiratory muscles are acting, often powerfully, has stimulated a lot of research, and a cloud of misconception. Now, with more careful study, the clouds are clearing, but the view is far from simple. Clearly, the abdominal muscles have an important role in the breathing pattern of the patient after abdominal surgery. It is not evident if the abnormalities in breathing, of themselves, require treatment, or how they could be altered if this were desirable. These changes in respiratory mechanics could conceivably be an appropriate and effective response to surgical trauma.[7] However, lung collapse and infection remain difficult problems for patients after abdominal surgery, and abnormalities in abdominal muscle activity may contribute to them: careful clinical physiological measurements and clear thinking are needed to tease out the links and develop effective therapies.

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EDITORIAL II

Animal tissues into humans

Because of concerns regarding the increased likelihood of organs from genetically modified animals soon being transplanted into humans in the UK, the Secretary of State for Health has established a group under the chairmanship of Professor Ian Kennedy. Its terms of reference were: "In the light of recent and potential developments in xenotransplantation to review the acceptability of and ethical framework within which xenotransplantation may be undertaken and to make recommendations". This group has now reported.[1]

Clinical procedures involving xenotransplantation demonstrate several problems associated with this technique: ethics, physiological differences, immunological rejection and infection. Heart, kidney, liver, lungs, islets of Langerhans (pancreas), neural tissue, bone marrow, skin, cornea, blood and gene therapy are of current transplant interest.

Reemtsma, McCraken and Schlegael showed in 1964 that renal transplantation from chimpanzee to humans could provide long-term function.[2] In 1994, Groth and colleagues reported the survival of porcine pancreatic endocrine tissue in 10 diabetic patients.[3] A baboon-to-human bone marrow transplant in a patient with AIDS was reported in the USA in 1996 but failed to engraft.[4] Starzl and co-workers from Pittsburgh reported a baboon-to-human liver transplant which survived without significant rejection for 70 days in a patient with HIV and hepatitis B virus associated with chronic active hepatitis.[5] In the USA one research group has received approval from the Food and Drug Administration (FDA) to use livers from genetically modified pigs as *ex vivo* support for patients with liver failure waiting for human organs to become available. In the UK, at least one company is developing genetically modified pigs for use as source animals for xenotransplantation. In September 1995, one UK company announced the results of research involving the heterotopic transplant of pigs' hearts into cynomologous monkeys.[1] They have indicated that it is their intention to move to xenotransplants involving humans over the next 12 months. The Nuffield Council on Bioethics has recently given its approval in a report on xenotransplantation for pig organs to be transplanted into humans.[6] The council also called for a statutory advisory committee to be in place before the first xenotransplants are carried out in humans.

Possible harms surrounding xenotransplantation that were identified by the group include:

(1) effects on the animal of genetic modification and effects on the human of transplantation;
(2) possible excess suffering of patients when the transplanted tissue does not function or the possible harm to future humans by the introduction of new virus strains;
(3) possible suffering of the animals involved;
(4) diversion of research away from techniques which may eventually improve the shortfall in human tissue availability;
(5) diversion of funds from other areas of health care.

Not all animals are an appropriate source of organs and tissue for transplantation into humans. The appropriateness of the choice of animal depends on several factors. The anatomical, physiological and genetic characteristics of the animal are crucial. The animal species chosen must be easily bred in large numbers, possibly in special pathogen-free environments. There is a real risk of the animal acting as a vector for transmission of infection to humans. In addition, there is the ethical acceptability of using a particular animal for the purpose of producing organs for transplantation to humans.

Clearly, there are also different cultural and religious backgrounds and beliefs which make the use of either some or no animals suitable for xenotransplantation. This is either because of ethical objections to the use of animals in this way, or the unacceptableness of the transplant procedure itself. Is it ethically justifiable? Religious and secular thinking in the West have tended in the past to give animals a low status. It is argued that humans have the capacity for autonomous action and are on that account "ends in themselves". Animals do not have this capacity and so their value is simply to be a means to human ends. However, there has been much recent popular interest in the rights of animals–the "green movement", the "animal rights movement" and the trends to vegetarianism and "not tested on animals" policies seen with some products.

The group's view was that animals do have rights and while there is no fundamental right not to be used for xenotransplantation, animals should not be so used in circumstances which violate unjustifiably the minimum rights they may have. Their interests must be considered in any assessment of the benefits and harms arising from the introduction of xenotransplantation. The group considered that animals vary a great deal in their complexity and presumably in their capacity for suffering. Primates are at the higher end of this scale, and have close affinities with humans, in particular their mental capacity, self-awareness and capacity for suffering. They consequently argued that it would be ethically unacceptable to use primates as source animals for xenotransplantation. The arguments that ruled out primates did not however, rule out the pig. The balance of potential benefits to humans *vs* the harm involved to the pig was such that the group felt it acceptable to use the pig for xenotransplantation.

Not all xenotransplantation procedures involve genetic modification of animals. However, all other aspects being met, what are the limits of acceptable genetic modification? Does such modification change the entity from what it was, and does it harm the animal? The group considered that there should be concomitant benefit to humans, and the pig should neither suffer unduly nor cease recognizably

Table 1 Organisms of concern in the UK that cannot be guaranteed to be absent from a xenograft organ[1]

- Viruses that are known to infect pigs
  - Porcine retrovirus
    - Porcine polyomavirus
    - Porcine parvovirus
    - Porcine congenital tremor virus
    - Porcine cytomegalovirus
    - Porcine reproductive and respiratory syndrome (PRRS) virus
    - Influenza virus
  - Viruses potentially infective in pigs
    - Borna disease virus
    - Hantovirus
    - Senai virus (parainfluenzovirus 1)
  - Bacteria
    - *Leptospira bratislava* and *muenchen* (kidney)
    - *Pseudomonas pyocyanea*
    - *Bordetella bronchiseptica* (lungs)
    - *Salmonella* spp
    - *Pasteurella multocida* (lungs)
    - *Actinobacillus pleuropneumoniae* (lungs)
    - *Mycoplasma hyopneumoniae* (lungs)
  - Parasites
    - *Toxoplasma*
    - *Neospora*
    - *Cryptosporidium*
  - Prions

to be a pig. Constant monitoring of the animals which have been modified and assessments of the proposed genetic modifications are both required.

Ethical issues apart, infection is the next single most important aspect of xenotransplantation. Assuming that the transplant were to function correctly and not be rejected, there would always remain the possibility that an infection could be transmitted from the source animal to the recipient, or perhaps more worrying to the wider population (table 1).

Viruses pose the greatest risk of infection—both known and unknown. The group considered it unsafe to proceed with clinical studies at the current time as there is insufficient knowledge about known viruses. When such data are available they suggest that a system should be in place to monitor the emergence of any unusual disease or any unknown pathogens and to require, as a consequence, that appropriate additional research be completed.

The group's major recommendation was the establishment of a National Standing Committee backed by legislation. This committee would have overall national responsibility for overseeing the development of xenotransplantation; that is the transplant of viable, replicating animal tissue into humans. It would set standards and ensure their implementation. The committee would co-ordinate its activities with those of the local research and ethics committees (LREC) and any proposal for research into xenotransplantation involving humans would be approved by the National Standing Committee before approval by a correctly constituted LREC. The power of the National Standing Committee would be exercised through the local research and ethics committees.

There is already in place legislation covering some aspects of the recommendations, namely the Animals (Scientific Procedures) Act 1986. This in particular covers the types of animal used and the extent of harm or suffering considered acceptable, in addition to the detailed manner in which such animals are bred and housed. The Government was, however, in broad agreement with the recommendations of the group and has established the UK Xenotransplantation Interim Regulatory Authority (UKXIRA) to be chaired by Lord Habgood. The Secretary of State has welcomed views and has initiated a wider consultation of the proposals.

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CLINICAL INVESTIGATIONS

Pulmonary function and pain after gastroplasty performed via laparotomy or laparoscopy in morbidly obese patients†

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Summary

We have compared severely obese patients (body mass index >35 kg m^{-2}) undergoing laparoscopic or open gastroplasty ($n = 15$ in each group) to determine if laparoscopy results in any benefit in the obese. Postoperative pain, measured on a 100-mm visual analogue scale, and opioid consumption were recorded during the first two days after operation. Tests of pulmonary function were performed and Sp_{O_2} was measured 4 h after surgery and on days 1, 2 and 3 after operation. Pain at rest was similar in the two groups, but in the laparoscopy group, requirements for postoperative opioid were 50% less ($P < 0.05$). Pain intensity during mobilization and on coughing was significantly less after laparoscopy (differences between mean pain scores in both groups ranged from 20 to 32 mm during mobilization and from 32 to 34 mm during coughing). Forced vital capacity, forced expiratory volume in 1 s and peak expiratory flow rate were reduced significantly less after laparoscopic gastroplasty than after open gastroplasty (on day 1 forced vital capacity was reduced by 50% compared with 64%, forced expiratory volume in 1 s was reduced by 50% compared with 66% and peak expiratory flow rate by 45% compared with 60%). Sp_{O_2} values were significantly greater in the laparoscopy group (day 1: mean 95 (SD 2) % *vs* 91 (5) %; day 3: 97 (1) % *vs* 94 (3) %). This study suggests that the beneficial effects observed after laparoscopic gastroplasty in morbidly obese patients were similar to those reported after laparoscopic cholecystectomy in non-obese patients. (*Br. J. Anaesth.* 1998; **80**: 283–288)

Keywords: lung, function; complications, obesity; pain, postoperative; surgery, laparoscopy; surgery, laparotomy

Obesity results in multiple pathophysiological disturbances, including cardiovascular, respiratory, gastrointestinal, metabolic and pharmacological changes. These changes complicate perioperative anaesthetic and surgical management of obese patients. Consequently, postoperative morbidity and mortality are higher in obese than in non-obese patients.[1 2] Obesity significantly increases the risk of postoperative hypoxaemia and pulmonary complications, particularly after upper abdominal surgery.[3 4] These observations are clinically relevant as up to 23% of the population in Europe and 33% in the USA is obese, and almost 5% of the USA population weigh more than twice their ideal body weight.[5 6] Furthermore, morbidly obese patients are frequently scheduled for abdominal surgery, such as gastroplasty, to treat diet-resistant obesity.

Laparoscopic cholecystectomy results in less postoperative pulmonary dysfunction,[7–12] faster recovery of preoperative pulmonary function[10] and less atelectasis[9 10] than open laparotomy. Postoperative pain or opioid requirements, or both, are also reduced after laparoscopy.[7 8 11–13] All of these postoperative benefits facilitate early chest physiotherapy, mobilization and ambulation, which may be particularly beneficial for obese patients.[2] Laparoscopic cholecystectomy, initially considered to be contraindicated in obese patients for technical reasons, is now performed regularly in these patients and is associated with similar postoperative clinical benefits to those reported in non-obese patients. These include earlier resumption of diet, reduced duration of hospitalization and fewer complications compared with laparotomy.[14–18] Nevertheless, the benefits of laparoscopy on postoperative pulmonary dysfunction may be less in obese patients. Indeed, we observed that pulmonary function tests in morbidly obese patients after open gastroplasty[19] were affected to a greater degree than in non-obese patients after open cholecystectomy.[7–12] Similarly, Johnson and colleagues reported that improvement in postoperative pulmonary restrictive syndrome observed after laparoscopy might be less in obese than in non-obese patients.[9] However, they included only eight moderately obese patients. To our knowledge, no studies have explored the pathophysiological changes after laparoscopy in morbidly obese patients.

The laparoscopic approach has now been extended to gastroplasty.[20] Therefore, we compared prospectively postoperative pain and pulmonary function after gastroplasty performed via laparoscopy or laparotomy in severely and morbidly obese patients, to determine the potential benefits of the laparoscopic approach compared with the open procedure.

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Patients and methods

The study was conducted after obtaining approval from our institution's Ethics Committee and informed consent from all patients. We studied 15 consecutive patients undergoing elective laparoscopic gastroplasty and 15 undergoing open gastroplasty. These patients had suffered severe obesity (body mass index (BMI) greater than 35 kg m^{-2}) for more than 5 yr and were resistant to dietary treatment under medical control. None of these patients had cardiac or intrinsic pulmonary disease.

We used the same anaesthetic technique in all patients. Anaesthesia was induced with clonidine 0.3 mg i.v. given over 10 min, propofol 2 mg kg^{-1} i.v. and sufentanil 20 µg i.v. Orotracheal intubation was facilitated by succinylcholine 1 mg kg^{-1}. General anaesthesia was maintained with isoflurane and 50% nitrous oxide in oxygen. Intraoperative neuromuscular block was produced with atracurium. At the end of surgery, residual neuromuscular block was antagonized with neostigmine 2.5 mg and atropine 1 mg.

Open gastroplasty consisted of reduction of the stomach with creation of a small pouch using four vertical rows of staples associated with a silastic ring, as described by Laws.[21] Gastric resection was not performed. Gastroplasty was performed via a midline incision extending from the xiphoid notch to the umbilicus. In the laparoscopy group, an adjustable silicone gastric band (Inamed, Breda, The Netherlands) was used to create a small upper gastric pouch of 15 ml in volume.[20] The surgical approach (laparotomy *vs* laparoscopy) was determined by the patient's acceptance of the laparoscopic technique and agreement by the patient to pay for the silicone band used for laparoscopic gastroplasty. It should be noted that in Belgium, laparoscopic gastroplasty costs patients three times more than laparotomy. No patient in either group had a nasogastric tube after operation.

POSTOPERATIVE ANALGESIA

All patients received the same postoperative analgesic therapy: i.v. patient-controlled analgesia (PCA) with piritramide, a synthetic opioid (Dipidolor, Janssen Pharmaceutica, Beerse, Belgium) combined with i.v. administration of propacetamol, a precursor of paracetamol, 2 g every 6 h (Prodafalgan; UPSA Medica, Brussels, Belgium: propacetamol 2 g = paracetamol 1 g). PCA settings were: bolus dose = piritramide 1 mg, lockout interval = 5 min, maximum dose = 20 mg every 4 h; no continuous infusion was used. Patients were instructed before operation in the use of the PCA pump. Pain scores were recorded on a 100-mm visual analogue scale at rest, during mobilization (patients were asked to move from the supine to the sitting position) and on coughing. Pain intensity was measured 4 h after surgery, at 08:00, 13:00 and 18:00 on day 1, and at 08:00 on day 2 after operation. Postoperative piritramide consumption was measured every 4 h until 40 h after operation.

PULMONARY FUNCTION

Pulmonary function testing was performed in the sitting position by the same technician who was blinded to the patient allocation group, on the day before surgery, 4 h after surgery and on days 1, 2 and 3 after operation. The following variables were recorded: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV$_1$) and peak expiratory flow rate (PEFR). These variables were measured using a Microlab 3000 series bedside spirometer (Micro Medical Ltd, Rochester, England). Capillary haemoglobin oxygen saturation Sp_{O_2} was also measured using a Datex Cardiocap pulse oximeter (Datex, Helsinki, Finland) after breathing room air for 15 min. Patients in both groups had the same regimen of chest physiotherapy combined with incentive spirometry after operation.

Table 1 Patient data, duration of surgery (mean (SD or range) or number) and duration of hospital stay (median [range]) in patients undergoing laparoscopic or open (laparotomy) gastroplasty. *P<0.05 compared with laparotomy group

	Laparoscopy group	Laparotomy group
Age (yr) (mean (range))	33 (23–44)	32 (19–52)
Weight (kg)	113 (14)	109 (14)
Height (cm)	166 (6)	163 (7)
Body mass index (kg m^{-2})	41.2 (5.2)	40.9 (4.2)
Sex (F/M)	14/1	13/2
Duration of surgery (min)	137 (39)*	83 (30)
Smoker (Y/N)	10/5	7/8
Postop. hospital stay (days)	4 [4–5]	4 [4–6]

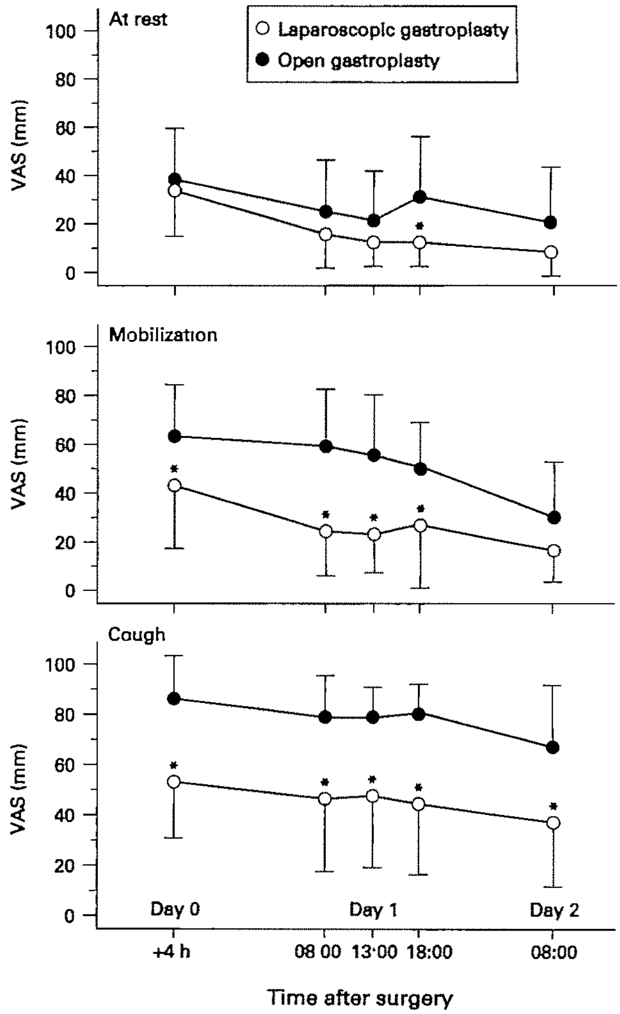

Figure 1 Pain intensity (mean (SD)) at rest, during mobilization and on coughing after laparoscopic or open gastroplasty. Pain was measured using a 100-mm visual analogue scale (VAS). *P <0.05 compared with the laparotomy group.

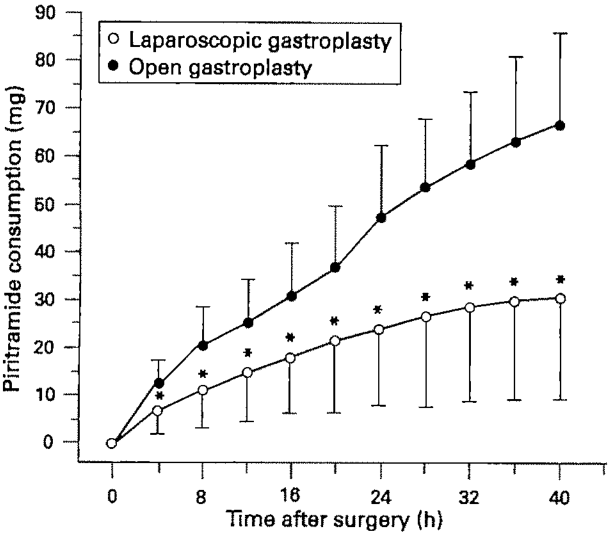

Figure 2 Cumulative postoperative piritramide consumption (mean (SD)) recorded from a patient-controlled analgesia pump after laparoscopic or open gastroplasty. $^*P < 0.05$ compared with the laparotomy group.

STATISTICAL ANALYSIS

Results are reported as mean (SD). Data were analysed by two-way analysis of variance followed by Scheffé's test. Patient data were compared using the unpaired Student's *t* test or the Mann–Whitney test, where appropriate. Results were considered statistically significant at the 5% critical level.

Results

Patient characteristics and duration of hospital stay were similar in the two groups. Nine patients in the laparoscopy group and 11 patients in the laparotomy group had a BMI greater than 40 kg m^{-2}. Duration of surgery was significantly longer in the laparoscopy than in the laparotomy group (table 1).

Pain intensity at rest, during mobilization and on coughing decreased significantly over time in both groups after surgery. Pain scores at rest were similar in the two groups, except at 18:00 on day 1 when patients in the laparotomy group reported significantly more pain than those in the laparoscopy group. Pain during mobilization and on coughing was significantly more intense in the laparotomy group throughout the study (fig. 1). Opioid consumption was significantly reduced in the laparoscopy group as early as 4 h after surgery (fig. 2). Interestingly, whereas opioid consumption decreased significantly over time after laparoscopy, a significant increase in opioid consumption was observed in the laparotomy group 20 h after surgery, which corresponded to the morning of the first day after operation.

FVC, FEV_1 and PEFR decreased significantly in the two groups after operation. However, FVC, FEV_1 and PEFR were significantly higher in the laparoscopy group than in the laparotomy group at each time after surgery. Furthermore, the rate of recovery towards preoperative values for these three variables was significantly faster in the laparoscopy group, particularly for FEV_1 and PEFR (fig. 3). Sp_{O_2} values were significantly decreased in both groups 4 h after surgery and on the first day after operation. However, the laparoscopy group had a significantly higher mean Sp_{O_2} on the first and third days after operation (fig. 4).

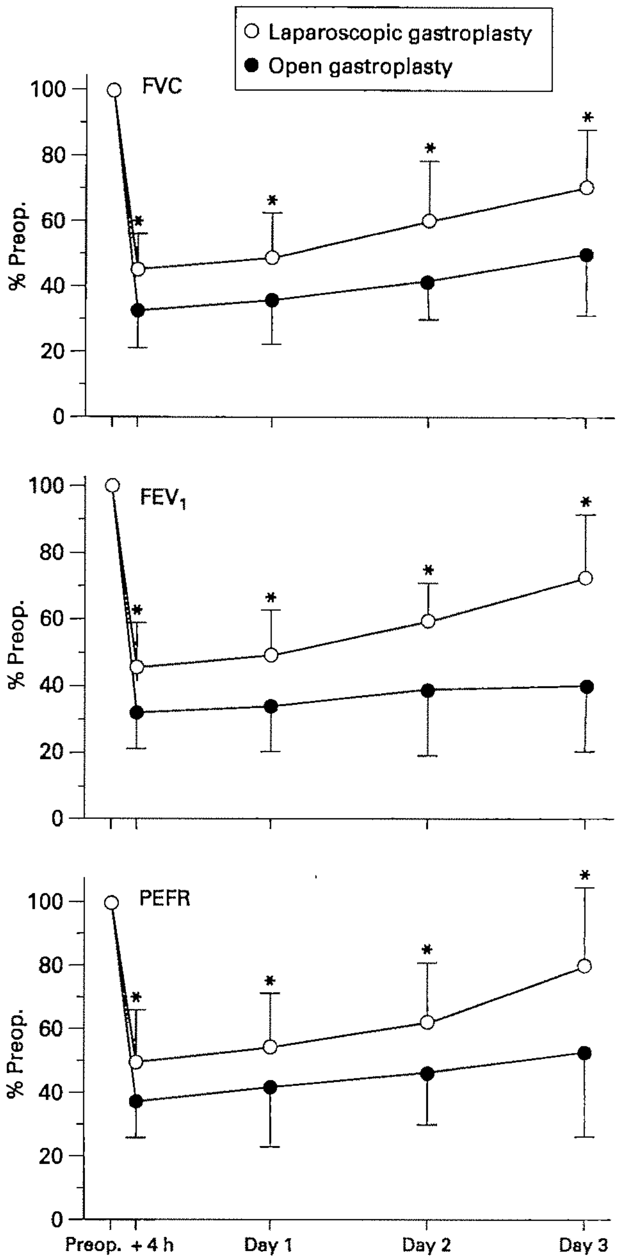

Figure 3 Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and peak expiratory flow rate (PEFR) after laparoscopic or open gastroplasty. Data (mean (SD)) are expressed as percentage of preoperative values. $^*P < 0.05$ compared with the laparotomy group. The rates of recovery of FVC, FEV_1 and PEFR were steeper in the laparoscopy than in the laparotomy group.

Discussion

This study has demonstrated that laparoscopic gastroplasty resulted in less postoperative pain, reduced opioid consumption and less postoperative pulmonary dysfunction compared with open gastroplasty. These findings suggest that severely (BMI 35–40 kg m^{-2}) and morbidly (BMI 40–50 kg m^{-2}) obese patients benefit from similar advantages after laparoscopy to those observed in non-obese patients.

Pain at rest did not differ between the two groups except at 18:00 on the first day after operation. Indeed, as patients in both groups were provided with PCA, they could titrate opioid administration to

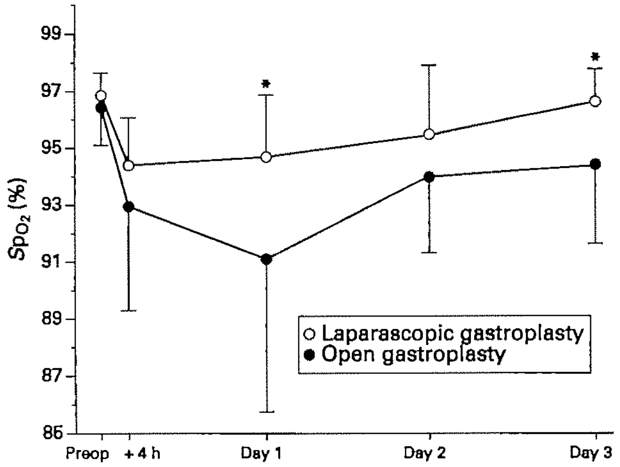

Figure 4 Capillary haemoglobin oxygen saturation Sp_{O_2} (mean (SD)) after laparoscopic or open gastroplasty. $*P < 0.05$ compared with the laparotomy group.

obtain similar levels of presumably satisfactory analgesia at rest. However, opioid requirements to reach this level of analgesia were significantly less after laparoscopy. After laparotomy, continual stimulation of the abdominal wall incision results in persistent pain and consequently greater opioid consumption. Patients, although in bed for the first 20 h after operation, were more mobile and active on day 1, leading to increased nociception. Accordingly, an increase in opioid consumption was observed in the laparotomy group 20 h after operation. Conversely, laparoscopy does not involve a large surgical incision and spares the abdominal wall the trauma of surgical retractors. Consequently, parietal pain is reduced after laparoscopy and is also more short-lived.[22] Moreover, movement, coughing and ambulation result in less pain, and opioid consumption continues to decrease on day 1. The reduction in opioid consumption observed after laparoscopy is particularly useful in obese patients who are thought to be more sensitive to the side effects of opioid analgesia than non-obese patients.[1]

The pathogenesis of postoperative pulmonary restrictive syndrome seen after laparotomy includes several factors, such as the site and size of incision,[23 24] postoperative pain[23 25] and diaphragmatic dysfunction.[26–28] Abdominal wall trauma and postoperative pain are reduced significantly after laparoscopy.[7 8 11 13] Moreover, diaphragmatic impairment is also less after laparoscopy than after laparotomy.[29–31] Consequently, laparoscopy results in less postoperative pulmonary dysfunction.[7–12] Our study showed that the reduction in pulmonary dysfunction reported after laparoscopy in non-obese patients is also present in severely and morbidly obese patients. This effect was observed despite longer surgical times in the laparoscopy group. Furthermore, the slopes of the recovery curves for FVC, FEV_1 and PEFR were steeper in the laparoscopy group than in the laparotomy group. The faster recovery to preoperative values may result from differences in pain characteristics after these two surgical approaches. Parietal pain, which affects effort-dependent spirometric volumes is not only less intense, but more short-lived after laparoscopy than laparotomy.[7 22] Similarly, duration of diaphragmatic dysfunction also seems to be shorter after laparoscopy.[30 31] Moreover, the reduction in pain and opioid consumption observed after laparoscopy may facilitate chest physiotherapy, early mobilization and ambulation, all of which help to prevent the development of postoperative atelectasis and secondary hypoxaemia.[32–34]

This study has confirmed that pulmonary function tests after open upper abdominal surgery were affected to a greater degree in obese[19] than in non-obese patients.[7–12] Similarly, the decrease in pulmonary volumes measured after laparoscopy in our obese patients were greater than those reported in non-obese counterparts.[7–12] Several mechanisms may contribute to the more severe postoperative pulmonary restrictive syndrome observed in obese patients. Obesity is associated with reduced functional residual capacity.[35] The magnitude of the decrease in functional residual capacity required for spontaneous ventilation to decrease within the closing volume is, therefore, less in obese than in non-obese patients.[4 36] As a consequence, the postoperative decrease in lung volumes is more likely to result in gas trapping, atelectasis and hypoxaemia. Even small postoperative changes may produce more significant effects in these patients. Diaphragmatic dysfunction is one of the main determinants of the postoperative restrictive syndrome.[26 27] Because of reduced thoracopulmonary compliance in obese patients,[37] the pressure gradient generated by impaired diaphragmatic contraction (even if similar in obese and non-obese patients) would result in mobilization of smaller lung volumes. Finally, respiratory muscle work load is increased and the efficiency of breathing is decreased in obese patients.[38] Postoperative fatigue would further aggravate these pathophysiological changes and impair muscle performance.[39] Lung volumes measured by spirometry would be reduced in obese compared with non-obese patients. Nevertheless, the rate of improvement in pulmonary function observed after laparoscopy (relative to that seen after laparotomy) in the morbidly obese patient is clinically significant, as Sp_{O_2} values were significantly higher after laparoscopy than after laparotomy. Our study was not designed to reveal any benefit of laparoscopy on the incidence of postoperative pulmonary complications in morbidly obese patients. Therefore, we did not perform postoperative chest x-ray. This important clinical issue deserves to be investigated.

We do not believe that the benefits observed in the laparoscopy group resulted from differences in socio-economic class or from different levels of patient motivation between the two groups. Indeed, approximately 80–90% of the obese patients from both groups belonged to the lower socio-economic classes, as has been reported previously.[5] Although the cost difference between the two surgical approaches did not allow us to perform a randomized study, agreement to pay for the silicone band was not the primary indication for selection of surgical technique. This study was conducted soon after the development of laparoscopic gastroplasty, while the open procedure was still more popular and performed more frequently than laparoscopic surgery. Many obese patients were persuaded to choose open gastroplasty by relatives who successfully underwent this procedure, or after information received from various associations of morbidly obese patients.

Several dietary treatments had already failed in these patients, who had suffered severe obesity for more than 5 yr. For all of these reasons, motivation was high in each patient, and was similar in the two groups.

This study was carried out 6 months after the introduction of laparoscopy for gastroplasty in our institution. The surgical team was therefore still learning this laparoscopic procedure. With experience, a reduction in duration of surgery and surgical trauma can be expected. Consequently, the magnitude of the benefits observed after laparoscopic gastroplasty on postoperative pain and pulmonary dysfunction may be increased further. Because hospital stay after gastroplasty is standardized and dependent mainly on patient adaptation to the small gastric pouch, we did not observe a significant effect of laparoscopy on this variable. Further studies are necessary to compare postoperative weight loss and the incidence of early and late surgical complications after these two surgical approaches.

In summary, severely and morbidly obese patients undergoing laparoscopic gastroplasty had significantly less postoperative pain, required less opioid and had better pulmonary function after operation compared with conventional open gastroplasty. All of these benefits are particularly welcome in these patients who are at high risk of developing postoperative pulmonary complications.

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Extradural S(–)-bupivacaine: comparison with racemic RS-bupivacaine†

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Summary

Bupivacaine has a chiral centre and is currently available as a racemic mixture of its two enantiomers: R(+)-bupivacaine and S(–)-bupivacaine. Preclinical studies have demonstrated that there is enantiomer selectivity of action with the bulk of central nervous system and cardiovascular toxicity residing with the R(+) isomer. The aim of this study was to compare the clinical efficacy and safety of S(–)-bupivacaine with racemic RS-bupivacaine for extradural anaesthesia. We studied 88 patients undergoing elective lower limb surgery under lumbar extradural anaesthesia who received 15 ml of 0.5% or 0.75% S(–)-bupivacaine, or 0.5% RS-bupivacaine in a randomized, double-blind study. There was no difference in onset time, maximum spread of sensory block or intensity of motor block between the three groups. Duration of sensory block was significantly longer for 0.75% S(–)-bupivacaine. We conclude that S(–)-bupivacaine has similar local anaesthetic characteristics to RS-bupivacaine when used for extradural anaesthesia. (*Br. J. Anaesth.* 1998; **80**: 289–293)

Keywords: anaesthetics local, bupivacaine, pharmacokinetics, stereoisomers; anaesthetic techniques, extradural

The structure of bupivacaine has a chiral centre and as a result it exhibits stereoisomerism.[1] It is available commercially as a racemic mixture (50:50) of its two enantiomers, dextrobupivacaine (R(+)-bupivacaine) and levobupivacaine (S(–)-bupivacaine). The two molecules are non-superimposable mirror images of each other and while they have identical physicochemical properties they have distinct pharmacological and toxicological effects.

Albright's editorial in 1979 first drew attention to the problems of cardiotoxicity related to bupivacaine.[2] There is mounting evidence from both *in vitro* and *in vivo* studies that the greater inherent cardiotoxicity resides with R(+)-bupivacaine. However, no work has been performed to ensure that this reduction in cardiotoxicity with S(–)-bupivacaine is not at the expense of reduction in clinical potency. The aim of this controlled, randomized, double-blind study was to investigate the clinical efficacy and dose response of S(–)-bupivacaine compared with standard racemic RS-bupivacaine in patients undergoing lower limb surgery under extradural anaesthesia. Aspects of drug safety were also studied in this first clinical study investigating S(–)-bupivacaine.

Patients and methods

After obtaining local Ethics Committee approval, we studied 96 patients (ASA I–II, aged 19–80 yr) undergoing elective lower limb surgery under extradural anaesthesia, recruited from three centres (48, 32 and 16 patients, respectively). After obtaining written informed consent, patients were allocated randomly to one of three groups. Each group received 15 ml, in a double-blind manner, of 0.5% or 0.75% S(–)-bupivacaine (Chiroscience, UK) or 0.5% RS-bupivacaine (Marcain, Astra).

Preoperative screening included a 12-lead ECG, urinalysis and blood for routine haematology and clinical chemistry. These were repeated in the postoperative period. Approximately 1 h after premedication with oral temazepam 10–20 mg, the patient was transferred to the anaesthetic room, venous access was established and an infusion of Hartmann's solution (maximum 500 ml) commenced. The patient was monitored by non-invasive arterial pressure measurement, continuous ECG (lead II) and pulse oximetry. With the patient in the lateral position, the skin was infiltrated with 1% lidocaine (maximum 3 ml) at the L2–3 or L3–4 interspace. The extradural space was identified in the midline with an 18-gauge or 16-gauge Tuohy needle using loss of resistance to saline. The study drug (3 ml) was administered through the needle as a test dose. After 5 min, if there was no evidence of intravascular or intrathecal injection, the remaining 12 ml of solution were injected in an incremental manner (4-ml aliquots injected over 15 s with 60 s

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Table 1 Patient characteristics (mean (SD or range) or number)

	0.5% S(–)-bupivacaine	0.75% S(–)-bupivacaine	0.5% RS-bupivacaine
n	29	30	29
Age (yr)	46 (20–75)	46 (24–76)	50 (19–80)
Sex (M/F)	10/19	8/22	13/16
Weight (kg)	72 (15)	70 (15)	75 (15)
Height (cm)	166 (10)	165 (10)	169 (11)

between each aliquot) such that total injection time was 7 min 45 s. After completion of injection (time zero), the needle was removed and the patient placed supine. Surgery was not commenced until at least 30 min after completion of extradural injection.

Upper and lower levels of analgesia were tested with a 27-gauge short-bevel dental needle, at 2 and 5 min after completion of injection and at 5-min intervals for 30 min. Thereafter sensory block was assessed at 30-min intervals until it was judged to have regressed completely. Lower limb motor block was recorded using the modified Bromage scale (0 = no paralysis, able to flex knee and ankle; 1 = unable to raise extended leg but able to flex knee; 2 = unable to flex knee but able to flex ankle; 3 = unable to move lower limb) at the intervals stated above. Methods of assessments were standardized between the three centres. Haemodynamic variables (arterial pressure and heart rate) were also recorded at the same times until complete regression of block. Episodes of hypotension (defined as greater than 30% reduction in systolic arterial pressure) were treated at the discretion of the anaesthetist according to the following procedure: methoxamine 2-mg increments if heart rate >90 beat min^{-1}, ephedrine 3-mg increments if heart rate 60–90 beat min^{-1}, atropine 0.3–0.6 mg if heart rate <60 beat min^{-1}.

Evaluation of sensory and motor block, as judged adequate for surgery, was made by the anaesthetist using a three-point scale: 0 = complete failure; 1 = unsatisfactory block (inadequate analgesia, inadequate relaxation or patients requiring a general anaesthetic because of agitation or restlessness) and 2 = satisfactory block. For statistical analysis complete failure and unsatisfactory block were considered together as failures and compared with the successes (satisfactory block).

Sedation, if requested by the patient, was provided by an infusion of propofol. Verbal contact was maintained with the patient and supplementary oxygen administered. If the block was deemed inadequate for surgery, a general anaesthetic was administered to the patient (propofol infusion supplemented with bolus doses of fentanyl 50 µg).

The results were analysed using the statistical package SAS (v6.07). The power of the study was calculated using an estimate of between-subject variability from a previous study, that is an SD associated with duration of sensory block of 60 min.[3] For a difference between groups in duration of sensory block of 45 min, the power of the study was 83%. The power was 97% if this difference was increased to 60 min. Analysis of variance and the Student's *t* test or Kruskal–Wallis non-parametric analysis of variance and *z* test were used to compare groups. To compensate for multiple comparisons a sequentially rejective Bonferroni–Holm method was used. Logistic regression was used to analyse the quality of block. All tests used a significance level of 5%.

Results

We recruited 96 patients but eight were withdrawn before administration of the study drug for the following reasons: failure to meet inclusion criteria (three patients), technical failure (two), operation cancelled (two) and withdrawal of consent (one). Therefore, 88 patients were suitable for evaluation on completion of the study. The three groups were similar, with no significant differences in mean height, weight or age (table 1).

All three solutions produced extradural block within 30 min (table 2). Segmental spread of sensory block was similar in the three groups. Mean onset times for loss of sensation to pinprick were 8 min for 0.5% S(–)-bupivacaine, 6 min for 0.75% S(–)-bupivacaine and 7 min for 0.5% RS-bupivacaine. Median maximum sensory block height was T8 in the 0.5% and 0.75% S(–)-bupivacaine groups and T7 in the 0.5% RS-bupivacaine group, and median time to reach this level was 25 min in all groups. Duration of sensory block was significantly longer in

Table 2 Summary of sensory block Time of onset and duration (mean (SD)), maximum cephalad spread, time to maximum spread and duration of individual dermatomes (median (range)). ANOVA and Student's *t* test: *$P<0.05$ compared with 0.5% RS-bupivacaine and 0.5% S(–)-bupivacaine; ††$P<0.01$ compared with 0.5% RS-bupivacaine and 0.5% S(–)-bupivacaine; ‡‡$P<0.01$ compared with 0.5% RS-bupivacaine

	0.5% S(–)-bupivacaine		0.75% S(–)-bupivacaine		0 5% RS-bupivacaine	
	Left	Right	Left	Right	Left	Right
Onset (min)	8 (5)	8 (5)	6 (4)	7 (4)	7 (4)	6 (4)
Duration (overall) (min)	377 (128)	369 (135)	460 (111)*	471 (126)††	345 (107)	337 (98)
T1	260 (100–595)		275 (150–440)		225 (108–475)	
L2	280 (138–529)		309 (160–459)		256 (110–445)	
L5	249 (948–590)		365 (65–683)‡‡		264 (125–443)	
S1	269 (110–620)		403 (98–730)‡‡		228 (125–388)	
S3	230 (155–385)		334 (90–590)‡‡		200 (105–340)	
Max. cephalad spread	T8 (T2–T12)		T8 (C6–T11)		T7 (C6–L2)	
Time to max cephalad spread (min)	25 (10–90)		25 (10–180)		25 (15–90)	

Table 3 Summary of motor block. Onset and duration (mean (SD)) and grade of motor block (median (range))

	0.5% S(–)-bupivacaine		0.75% S(–)-bupivacaine		0.5% RS-bupivacaine	
	Left	Right	Left	Right	Left	Right
n	15	13	23	22	19	20
Onset (min)	25 (23)	26 (24)	27 (35)	31 (45)	17 (7)	18 (6)
Duration (min)	185 (122)	205 (148)	256 (99)	255 (107)	192 (74)	185 (66)
Max. grade	1 (0–3)		1 (0–2)		0 (0–2)	

Table 4 Overall success of block (number of patients (%)). Groups 0 and 1 were considered together as treatment failures and group 2 as treatment success. No significant difference (logistic regression, P=0.71)

	0.5% S(–)-bupivacaine	0.75% S(–)-bupivacaine	0.5% RS-bupivacaine
Satisfactory block (2)	18 (62%)	23 (77%)	22 (76%)
Unsatisfactory block (1)	8 (28%)	5 (17%)	7 (24%)
Complete failure (0)	3 (10%)	2 (7%)	0

the 0.75% S(–)-bupivacaine group (P = 0.001 on the right, P = 0.016 on the left), with a mean duration of 460 min compared with 377 min for 0.5% S(–)-bupivacaine and 345 min for 0.5% RS-bupivacaine. Analysis of individual dermatomes demonstrated the block to be of longer duration in the lower lumber and sacral dermatomes.

There was no significant difference in onset time or grade of motor block between the three groups (table 3). However, in the 0.5% S(–)-bupivacaine group, 14 of 29 patients did not develop motor block and there was a trend in the 0.75% S(–)-bupivacaine group to have a longer duration of block.

There were no significant differences between the three groups in arterial pressure (systolic, mean and diastolic) or heart rate. There was a reduction in both heart rate and arterial pressure during the first hour, with a subsequent return to baseline values. Hypotension was observed in 18 patients, evenly distributed between the three groups. All episodes responded to the treatment described.

The overall success of block and its adequacy for surgery (i.e. a score of 2) was 62% in the 0.5% S(–)-bupivacaine group, 77% in the 0.75% S(–)-bupivacaine group and 76% in the 0.5% RS-bupivacaine group (P = 0.71) (table 4). Blocks described as unsatisfactory were evenly distributed between the three groups. Three patients in the 0.5% S(–)-bupivacaine group and two in the 0.75% S(–)-bupivacaine group had complete failure of block (a technical failure with drug not in the extradural space) and required general anaesthesia.

Adverse sequelae were reported to be definitely, probably or possibly related to the study medication, with similar numbers in each group. Hypotension was the most common side effect during surgery. Six patients developed difficulty with micturition in the postoperative period. Five patients described minor neurological abnormalities (three complained of areas of hypoaesthesia which were related to surgery and two of small areas of paraesthesia) all of which resolved quickly after operation. There were no serious adverse events recorded and all patients made a complete recovery. Haematology, clinical chemistry and urinalysis repeated on the first day after operation revealed only minor abnormalities which were not thought to be related to the study medication. A 12-lead ECG was also repeated and detected minor abnormalities not present on the screening ECG in five patients. In the 0.5% S(–)-bupivacaine group, one patient had a sinus tachycardia and another a sinus bradycardia with atrial ectopics; one patient in the 0.75% S(–)-bupivacaine group showed sinus tachycardia with minor T wave inversion and in the 0.5% RS-bupivacaine group one patient developed sinus tachycardia and another minor T wave inversion.

Discussion

This study demonstrated that S(–)-bupivacaine is a suitable drug for use in extradural anaesthesia as it produced a block clinically indistinguishable from the racemate. We demonstrated a significantly longer duration of sensory block with 0.75% S(–)-bupivacaine compared with 0.5% S(–)-bupivacaine and 0.5% RS-bupivacaine. Given the increased safety margin of S(–)-bupivacaine, the 0.75% concentration may be used more commonly in clinical practice. We have also shown a trend, although not statistically significant, towards less motor block with equivalent doses of S(–)-bupivacaine compared with RS-bupivacaine.

Although bupivacaine remains one of the most popular local anaesthetic agents, caution is required because of its toxicity profile, particularly in relation to the heart. This has led to withdrawal of the 0.75% concentration in obstetric practice and its complete withdrawal for i.v. regional anaesthesia.

Until recently, it was believed that there was no difference between the isomers in relation to nerve blocking potency,[4] but in 1992, Lee-Son and colleagues in an *in vitro* study of frog sciatic nerves showed R(+)-bupivacaine to be more potent than S(–)-bupivacaine at producing both tonic and phasic block (two and three times, respectively).[5] However, *in vivo* any intrinsic difference in potency of the isomers may be modulated by stereoselectivity of effect on blood vessels. Aps and Reynolds found S(–)-bupivacaine to produce longer duration of analgesia when injected intradermally in volunteers, with a greater incidence of pallor around the injection site.[6]

With regard to systemic toxicity, the LD_{50} (in rats and mice) of R(+)-bupivacaine is 30–40% lower than that of S(–)-bupivacaine.[4] The major cause of death is cardiotoxicity, manifested as cardiovascular collapse and arrhythmias, particularly ventricular fibrillation. It is unclear if this is a direct cardiac effect of the local anaesthetic, an indirect centrally mediated effect or a combination of the two.

Bupivacaine binds to cardiac Na^+ channels in a time- and voltage-dependent manner.[7] Its slow dissociation time from the channel, that is fast-in, slow-out, produces slowing of conduction of the action potential (manifested as prolongation of the PR and QRS intervals on the ECG), predisposing to the development of re-entrant arrhythmias. This effect on Na^+ conductance can be detected indirectly by measuring *V*max (upstroke velocity of the action potential). Vanhoutte and colleagues, in a study of guineapig papillary muscle, concluded that S(–)-bupivacaine reduced *V*max much less than R(+)-bupivacaine at different rates of stimulation and resting membrane potentials.[8] Valenzuela and colleagues confirmed this stereoselective effect on Na^+ channels using guineapig ventricular myocytes and illustrated a similar stereospecificity in cloned human cardiac K^+ channels, with R(+)-bupivacaine showing greater affinity.[9] [10] It would appear therefore, that when the two isomers are compared in cardiac tissue, R(+)-bupivacaine has a greater affinity for and dissociates more slowly from ion channels than S(–)-bupivacaine, thus predisposing to an enhanced potential for arrhythmias.

Mazoit, Boico and Samii compared the pharmacodynamics of the isomers of bupivacaine with the racemate on the heart using an isolated perfused rabbit heart model.[11] When given in equal doses, they found an increase in QRS duration in all three groups, which was maximal with R(+)-bupivacaine (236 ms compared with 194 ms for the racemate and 59 ms for S(–)-bupivacaine). All hearts in the R(+)-bupivacaine and racemate groups developed severe atrioventricular (AV) block compared with only two of six in the S(–)-bupivacaine group. Ventricular fibrillation subsequently occurred in 83%, 66% and 0% of R(+)-bupivacaine, racemate and S(–)-bupivacaine treated hearts, respectively. In an attempt to further clarify the precise mechanism of AV block, Graf and colleagues, using isolated perfused guineapig hearts, showed that R(+)-bupivacaine produced significantly longer AV delay than S(–)-bupivacaine and the racemate.[12] As they were unable to exhibit any stereoselectivity at the AV node itself, they concluded that this delay was caused by a stereoselective effect on the coupling mechanism between the AV node and the surrounding conduction tissue in the atria and ventricles. There is also some evidence that part of this stereoselectivity of effect on cardiac toxicity is not solely a direct effect on the myocardium but also an indirect, centrally mediated effect. Denson, Behbehani and Gregg compared the effects of the two isomers on the cell firing rate (CFR) of the nucleus tractus solitarius in the brains of anaesthetized rats after an i.v. bolus of R(+)-bupivacaine or S(–)-bupivacaine (equal doses).[13] Both isomers reduced CFR, but the time to maximum reduction was significantly longer with S(–)-bupivacaine. In addition, all animals in the R(+)-bupivacaine group died, while 10 of 12 animals given S(–)-bupivacaine survived. Malignant ventricular arrhythmias were seen in 33% of the R(+)-bupivacaine and none of the S(–)-bupivacaine treated rats.

Although care must be taken when extrapolating results from the above studies to the clinical setting, a volunteer study by Gristwood and colleagues validated many of these findings.[14] In a double-blind, crossover study, subjects (primed with lidocaine 7 days before testing) were given an i.v. infusion of either S(–)-bupivacaine or the racemate at 10 mg min^{-1} until symptoms of CNS toxicity were reported (or to a maximum of 150 mg). Both drugs were well tolerated, with mean doses of 56.1 mg and 47.9 mg for S(–)-bupivacaine and the racemate, respectively. The use of transthoracic electrical bioimpedance allowed measurement of cardiac function and myocardial contractility which demonstrated that levobupivacaine produced a significantly smaller reduction in stroke index, ejection fraction and acceleration index than the racemate.

In summary, we have shown that S(–)-bupivacaine produced extradural anaesthesia, with a block clinically similar to racemic bupivacaine. The reduced toxicity of S(–)-bupivacaine was, therefore, not at the expense of a decrease in clinical efficacy. We conclude that S(–)-bupivacaine promises to increase the margin of safety for extradural anaesthesia.

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Addition of clonidine or fentanyl to local anaesthetics prolongs the duration of surgical analgesia after single shot caudal block in children

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Summary

Caudal anaesthesia is indicated for surgical procedures lasting less than 90 min. Fentanyl and clonidine are known to prolong postoperative caudal analgesia, but there are no data on their effect on duration of surgical analgesia. We evaluated if the addition of clonidine or fentanyl to local anaesthetics prolonged the duration of surgical analgesia after single shot caudal block in children in a randomized, double-blind study. We studied 64 children, aged 6–108 months, undergoing bilateral correction of vesicoureteral reflux which was expected to last more than 90 min. Patients were allocated to one of four groups: group O received 1 ml kg^{-1} of a mixture of 0.25% bupivacaine with epinephrine and 1% lidocaine in equal parts; group F received the same mixture of local anaesthetics in addition to fentanyl 1 μg kg^{-1}; group C received the same mixture of local anaesthetics in addition to clonidine 1.5 μg kg^{-1}; and group C+F received the same mixture of local anaesthetics in addition to fentanyl 0.5 μg kg^{-1} and clonidine 0.75 μg kg^{-1}. Single shot caudal block was sufficient in only 57% of children in group O compared with 93% in groups C and F and 86% in group C+F (P = 0.035). Global assessment of anaesthesia, defined as the time from caudal injection to the first administration of analgesic (either during or after surgery), was significantly longer in the three groups of children who received additives compared with local anaesthetics alone (P = 0.035), but there were no differences between the three additive groups. Vomiting was observed only in children who received fentanyl. Addition of clonidine or fentanyl to local anaesthetics prolonged the duration of surgical analgesia of caudal block, allowing single shot caudal anaesthesia to be recommended for surgery lasting 90–150 minutes. Clonidine had some advantages over fentanyl as it did not produce clinically significant side effects. (*Br. J. Anaesth.* 1998; **80**: 294–298)

Keywords: anaesthetic techniques, regional, caudal; anaesthetics local; analgesia, paediatric; sympathetic nervous system, clonidine; analgesics opioid, fentanyl

Caudal anaesthesia is used commonly in paediatric practice for orthopaedic and genitourinary surgical procedures. This simple technique allows rapid recovery from anaesthesia together with effective postoperative analgesia. However, the mean duration of surgical analgesia provided by local anaesthetics is limited and thus single shot caudal anaesthesia is indicated only for surgery expected to last less than 90 min.[1 2] In longer surgical procedures, insertion of an extradural catheter may be required to achieve sustained analgesia. However, placement of an extradural catheter is time-consuming and more expensive than single shot caudal block, and may be associated with various technical problems such as difficulty in insertion, vascular damage or leaks. To overcome these problems, various drugs have been added to local anaesthetic solutions to prolong the duration of caudal anaesthesia provided by a single injection. Fentanyl, a lipophilic opioid, is added frequently to local anaesthetics in children, but its beneficial effects are debated.[3 4] Side effects, such as nausea, vomiting or respiratory depression, are not uncommon. Extradural clonidine produces analgesia by a non-opioid spinal mechanism. This α_2 agonist is devoid of opioid side effects but may produce excessive sedation, hypotension and bradycardia in adults.[5] In children, addition of clonidine to local anaesthetics prolongs the duration of postoperative analgesia after inguinal hernia repair[6] and minor orthopaedic surgery.[7] However, there are no data on the effect of clonidine or fentanyl on the duration of effective surgical analgesia. Therefore, in this double-blind, randomized, prospective study, we evaluated if addition of clonidine or fentanyl to a mixture of local anaesthetics prolonged the duration of surgical analgesia, thus allowing single shot caudal analgesia to be recommended for surgery lasting more than 90 min.

Patients and methods

The study was approved by the Ethics Committee (CCPPRB, Ambroise Paré, Paris) and written parental informed consent was obtained. We studied children undergoing bilateral correction of vesicoureteral reflux, a surgical procedure expected to last more than 90 min. All were scheduled to receive general anaesthesia combined with caudal extradural block. A sensory block up to T10 is sufficient for this surgical procedure as skin incision is performed in

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the subpubic space. Exclusion criteria were: contraindications to caudal anaesthesia; body weight greater than 25 kg; and ASA III or greater.

Children were premedicated 30–40 min before surgery with midazolam 0.4 mg kg^{-1} rectally or orally. Anaesthesia was induced by face mask with halothane and 60% nitrous oxide in oxygen. After placement of an i.v. cannula, the trachea was intubated without the use of a neuromuscular blocking agent and the lungs were ventilated mechanically (Servo 900 D, Siemens). Anaesthesia was maintained with isoflurane (0.6 MAC corrected for age). Caudal anaesthesia was performed in the lateral position with a 22-gauge lumbar puncture needle and one of the four different mixtures described below was administered on a weight-related basis into the caudal space.

Children were allocated randomly in one of four groups after induction of anaesthesia by opening a sealed envelope. Group O received 1 ml kg^{-1} of a mixture of equal parts of 1% lidocaine and 0.25% bupivacaine with epinephrine 1/200 000 (maximum dose 20 ml), with normal saline 0.1 ml kg^{-1} (the same volume as that required for additives in the other groups); group C received the same mixture of local anaesthetics in addition to preservative-free clonidine 1.5 μg kg^{-1}; group F received the same mixture of local anaesthetics in addition to preservative-free fentanyl 1 μg kg^{-1}; and group C+F received the same mixture of local anaesthetics in addition to clonidine 0.75 μg kg^{-1} and fentanyl 0.5 μg kg^{-1}. For each child, two different syringes were prepared by an anaesthetist not involved in the study; one contained the local anaesthetics and the second contained 0.1 ml kg^{-1} of either saline (group O) or the additives (other groups). The anaesthetist in charge of the patient and all nursing staff in the post-anaesthesia care unit (PACU) were blinded to the content of the solutions given extradurally.

Heart rate (HR) and systolic arterial pressure (SAP) were recorded before induction, after induction but before caudal anaesthesia, and then every 5 min after caudal anaesthesia. During surgery, adequate analgesia was defined by haemodynamic stability, as indicated by the absence of an increase in SAP or HR of more than 15% compared with baseline values obtained just before the surgical incision, with isoflurane concentration maintained at approximately 0.6 MAC (expired concentration <1%). An increase in HR or SAP within 15 min of skin incision indicated failure of caudal anaesthesia. If, more than 45 min after skin incision, HR or SAP increased by more than 15%, analgesia was considered inadequate and children received rescue opioid during operation (alfentanil 10 μg kg^{-1}). The need for rescue opioid was considered as the first end-point of the study and subsequent data obtained from those children were no longer considered. Fluid therapy was standardized during and after surgery. During surgery, children received lactated Ringer's solution 6 ml kg^{-1} h^{-1} with 1% dextrose, whereas 5% dextrose in 0.33 normal saline was given at a rate of 4 ml kg^{-1} h^{-1} in the PACU. The following times were recorded: time from caudal block to skin incision, time from caudal block to the end of surgery and time from discontinuing the volatile anaesthetic to tracheal extubation.

At the end of surgery, the trachea was extubated and children were admitted to the PACU. Analgesia, sedation, haemodynamic state and side effects were monitored in the recovery room until 6 h after caudal block. In children who did not receive opioids during operation, analgesia was evaluated every 30 min by CHEOPS[8] (children less than 5 yr of age) or a visual analogue scale (children older than 5 yr). Propacetamol 30 mg kg^{-1} was given i.v. when the CHEOPS score was greater than 6 or VAS was greater than 40 mm. Residual pain was reassessed 30 min later and nalbuphine 0.2 mg kg^{-1} i.v. was administered if pain scores remained unchanged. Times to administration of propacetamol and nalbuphine were recorded. The time from caudal block to the first postoperative analgesic administration (propacetamol) was the end-point for those children who did not receive alfentanil during surgery. Finally, global assessment of the duration of effective analgesia was performed by comparing the time from caudal block to administration of the first analgesic (either alfentanil during surgery or propacetamol after surgery).

Sedation was assessed every 30 min using a three-point sedation score: awake (0), drowsy (1) or asleep (2). SAP and HR were recorded every 30 min. Oximetry was monitored continuously and oxygen desaturation was defined as Sp_{O_2} <95%. The incidence of residual motor block was assessed on arrival in the recovery room. Urinary retention was not assessed, as a bladder catheter was left in place by the surgeon in all cases.

Before the study, the number of patients required in each group was determined after a power calculation according to data obtained from previous studies. It was assumed that duration of surgical analgesia with a mixture of local anaesthetics was 90 min (range 60–120 min),[1 2] and that addition of fentanyl would increase this time by 50%,[3 4] and clonidine by 100%, as demonstrated for postoperative analgesia.[6] The effects of fentanyl and clonidine were assumed to be additive.[9] According to this hypothesis, a sample size of 15 patients in each group was adequate with an alpha risk of 0.05 and a power of 0.8.

Continuous data were compared using one-way analysis of variance, followed by the Student–Newman–Keuls test (Statview, version 4.2). The chi-square test was used for nominal data. The global efficacy of the four techniques was analysed by survival curves using the Kaplan–Meier method followed by the logrank test.[10] The end-point for such analysis was the time to first administration of analgesia either during surgery or in the postoperative period. $P < 0.05$ was regarded as statistically significant. Continuous data are expressed as mean (SD).

Results

We included 64 children in the study but five children did not complete it because of failure of the caudal block (subcutaneous injection) in four patients and insufficient duration of the surgical procedure (80 min) in one patient. Data from 59 children were therefore analysed: 14 in group O, 15 in group F, 16 in group C and 14 in group C+F. Mean age, weight, time from caudal block to surgical incision, duration of surgery, duration of general

Table 1 Patient and clinical data (mean (SD or range)). No significant differences

	Group O	Group F	Group C	Group C+F
n	14	15	16	14
Age (months)	43 (16–81)	45 (22–78)	43 (6–108)	37 (8–100)
Weight (kg)	16 (3)	16 (4)	15 (5)	14 (4)
Time from caudal block to surgery (min)	22 (8)	26 (12)	21 (12)	26 (11)
Duration of surgery (min)	133 (52)	132 (35)	129 (26)	137 (48)
Duration of general anaesthesia (min)	177 (54)	183 (31)	173 (39)	184 (51)
Time to extubation (min)	10 (7)	7 (4)	7 (4)	10 (5)
SAP before induction (mm Hg)	106 (12)	101 (11)	109 (20)	98 (10)
HR before induction (beat min^{-1})	107 (11)	103 (19)	117 (12)	117 (25)

Table 2 Postoperative analgesia. Times (mean (SD)) from caudal injection to the first administration of propacetamol and nalbuphine in the PACU. Data are from patients who did not receive peroperative rescue alfentanil. No significant differences

	Group O	Group F	Group C	Group C+F
First administration of propacetamol (min)	174 (29) (*n*=8)	253 (105) (*n*=14)	265 (118) (*n*=15)	287 (130) (*n*=12)
First administration of nalbuphine (min)	190 (39) (*n*=6)	274 (100) (*n*=12)	328 (254) (*n*=12)	322 (153) (*n*=11)

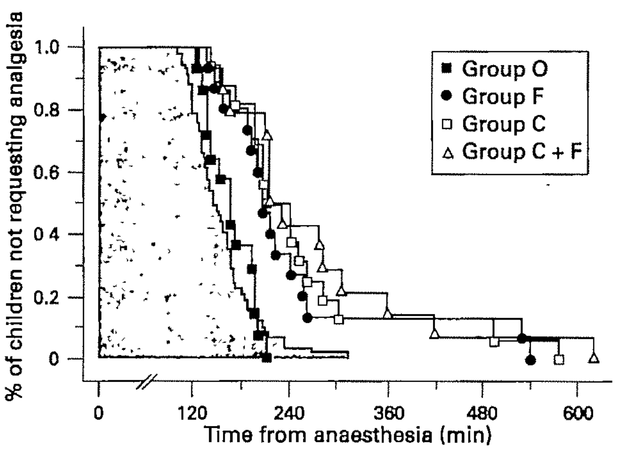

Figure 1 Effect of additives to local anaesthetics on duration of analgesia in the four groups. Time from caudal anaesthesia to first administration of analgesia either during surgery or in the postoperative period was significantly shorter in group O compared with the three other groups (logrank test = 0.035). Shaded area = actuarial curves of duration of surgery (caudal analgesia to end of surgery).

anaesthesia and time to extubation were similar in the four groups (table 1).

ANALGESIA

Surgical analgesia

Mean duration of surgery was 130 min in the four groups. Single shot caudal block provided adequate surgical analgesia in only 57% of children in group O compared with 93% in groups C and F and 86% in group C+F (chi-square test, $P = 0.035$). Six of 14 children in group O required rescue alfentanil during surgery compared with only one in group F, one in group C and two in group C+F. In patients in whom caudal block was not sufficient, alfentanil was effective in reducing SAP and HR close to baseline values.

Postoperative analgesia

Time to first postoperative analgesic administration was considered only in children who did not receive rescue alfentanil during surgery. There was a tendency for earlier analgesic requirements in group O, but this was not significant (table 2).

Global assessment

Mean duration of analgesia (defined as the time to first analgesia given either during or after operation) was significantly longer in the three groups who received additives compared with group O (245 (104) min in group F, 257 (118) min in group C, 271 (128) min in group C+F compared with 164 (30) min in group O) (ANOVA, $P = 0.035$), but no differences were observed between the three additive groups (C, F and C+F). The percentage of patients requiring analgesia as a function of time after caudal block is represented in figure 1.

HAEMODYNAMIC DATA

Baseline SAP and HR recorded before induction were similar in the four groups (table 1). Compared with baseline values, SAP decreased in all groups by 10–20% during anaesthesia, and increased by 5–20% during recovery (fig. 2). There were no significant differences in SAP profiles between the four groups. A similar decrease in HR was observed during anaesthesia in the four groups, followed by an increase during recovery. Higher values were observed during recovery in groups O and F compared with group C

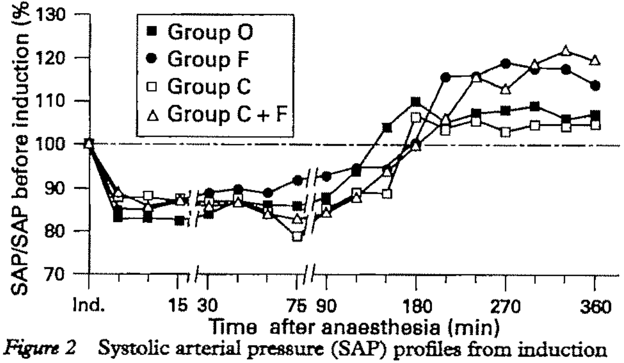

Figure 2 Systolic arterial pressure (SAP) profiles from induction (Ind.) to 6 h after caudal anaesthesia in the four groups. Changes in SAP are expressed as percentage of SAP before induction. For clarity, SD values have been omitted.

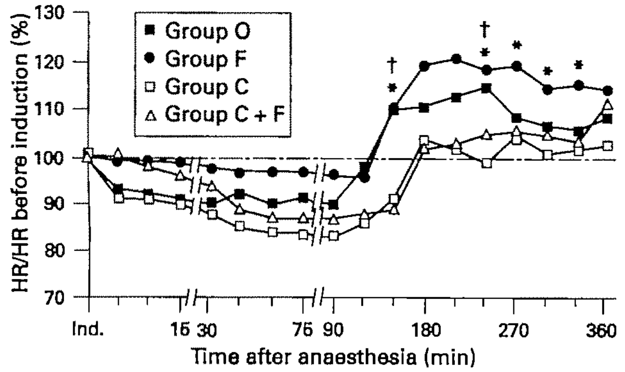

Figure 3 Heart rate (HR) profiles from induction (Ind.) to 6 h after caudal anaesthesia in the four groups. Changes in HR are expressed as percentage of HR before induction. For clarity, SD values have been omitted. $P < 0.05$: *group F *vs* group C; †group O *vs* group C.

when HR was expressed as a percentage of pre-induction values (fig. 3).

SIDE EFFECTS

Sedation scores, residual motor block on arrival in the recovery room and time to complete regression of motor block were similar in the four groups (table 3). A transient decrease in oxygen saturation to 92% was observed within the first hour of recovery in two children who received extradural fentanyl; one in a 54-month-old child in group F and the other in a 25-month-old child in group C+F. Vomiting was observed in the PACU only in children who received fentanyl (table 3). The addition of fentanyl to local anaesthetics increased significantly the incidence of vomiting compared with the two groups who did not receive fentanyl (groups O and C) (groups F and C+F *vs* groups O and C; $P = 0.011$).

Discussion

Our data demonstrated that addition of clonidine or fentanyl to a mixture of local anaesthetics prolonged analgesia provided by single shot caudal block. In paediatric anaesthesia, extradural analgesia via the caudal approach is used widely for many surgical procedures. The main disadvantage of this safe and reliable technique is short duration of action after a single injection of local anaesthetic. To avoid extradural catheter placement, and yet prolong the duration of single shot caudal anaesthesia, various additives to local anaesthetic solutions have been used.[11]

Fentanyl is added commonly to local anaesthetics administered in the extradural space to improve analgesia in the postoperative period.[12] However, few studies have addressed the benefit of fentanyl for single shot procedures. The addition of fentanyl produced only a slight change in the quality and duration of analgesia after administration of 2% lidocaine with epinephrine for a short surgical procedure[4] or after administration of 0.125% bupivacaine.[5] Therefore, it was concluded that addition of fentanyl to local anaesthetics offered no advantage over administration of local anaesthetics alone for short surgical procedures in children.

Several paediatric studies have already demonstrated that clonidine added to bupivacaine,[6 7] mepivacaine[13] or lidocaine[14] increases the duration and quality of postoperative analgesia provided by caudal anaesthesia. However, these studies were performed in children undergoing minor surgical procedures of short duration (<90 min) and there are no data on the effects of clonidine for more complex surgical procedures. Optimal extradural doses of clonidine are not well determined. In children, doses of 1 $\mu g\ kg^{-1}$ [6], 2 $\mu g\ kg^{-1}$ [7 13 15] or 3 $\mu g\ kg^{-1}$ [14] have been used without adverse respiratory or haemodynamic effects, while a decrease in SAP and HR was observed after a dose of 5 $\mu g\ kg^{-1}$.[16] In a preliminary study involving 70 children, we tested a dose of 1.5 $\mu g\ kg^{-1}$ which provided effective pain control without any clinical side effects.[17]

In our study, addition of fentanyl or clonidine was effective in increasing the duration of surgical analgesia, but we were unable to demonstrate a difference in efficacy between the three mixtures. Indeed, the SD of time to first analgesia was nearly four times greater in groups C, F and C+F than in the control group. As a result, the power achieved for the comparison of the three mixtures was extremely low (the power of this study was only 0.05 and 2000 patients would have to be included to demonstrate a significant difference between clonidine and fentanyl in terms of analgesic efficiency). One reason for such unexpectedly wide inter-individual variability may be related to the difficulties in predicting and assessing pain in the postoperative period in young children. Indeed, pain intensity and analgesic requirements may vary 5–7-fold in the postoperative period for the same surgical procedure.[18] Although all children underwent the same surgical procedure, postoperative pain remains a phenomenon that may vary greatly between individuals. Most children required supplementary analgesia in the PACU. In the clonidine group, mean time from caudal injection to first administration of an analgesic was shorter than in previous studies in which a bupivacaine–clonidine mixture was used,[6 7 15] similar to that of a mepivacaine–clonidine mixture[13] and longer than that of a lidocaine–clonidine mixture.[14]

Respiratory depression is an expected yet undesirable side effect of extradural opioids[19]; it has also been described in adults receiving extradural clonidine 300 μg.[20] In children, no respiratory depression

Table 3 Incidence of side effects. Number of patients with residual motor block on arrival in the PACU (and time to regression of motor block (mean (SD))), respiratory depression or vomiting, compared with the number of patients in each group. No significant differences

	Group O	Group F	Group C	Group C+F
Residual motor block on arrival in the PACU	3/14	4/15	4/16	5/14
Time to complete regression of motor block (min)	186 (32)	204 (38)	246 (25)	209 (18)
Respiratory depression				
Sp_{O_2} <95%	0/14	1/15	0/16	1/14
Vomiting	0/14	4/15	0/16	2/14

had been reported after caudal administration of fentanyl[3,4,21] or clonidine.[6,7,14,16] In this study, two transient decreases in arterial haemoglobin saturation to 92% were observed, both in children who received extradural fentanyl.

A sedative effect had been reported after extradural clonidine in adults[20] and to a lesser extent in children.[6,7] In this study, extubation times and sedation scores did not differ in the four groups. This lack of residual sedative effect may be explained by the length of time which elapsed from caudal injection to the first sedation score (mean 3 h).

The risk of hypotension and bradycardia is an expected side effect of extradural clonidine in adults.[5] Haemodynamic effects of extradural clonidine are less pronounced in children than in adults, and may depend on the dose administered.[6,7,16] Similar arterial pressure profiles were observed in the four groups of children in this study, as reported previously after extradural bupivacaine with or without epinephrine or clonidine.[6] The increase in heart rate observed during the recovery period was less marked in the two clonidine groups compared with groups O and F. This may be because of a direct effect of clonidine or may reflect more effective analgesia.

Finally, vomiting was observed only in children who received fentanyl extradurally. The emetic effect of extradural opioid is well known and involves supraspinal mechanisms, while clonidine exhibits antiemetic properties when administered by the oral[22] or i.v.[23] route. This may be an argument for the use of clonidine rather than fentanyl as an additive to local anaesthetics when prolongation of analgesia is required.

In summary, addition of clonidine or fentanyl or a mixture of both drugs to local anaesthetics prolonged the duration of surgical analgesia after a single shot caudal injection, thus allowing single shot caudal anaesthesia to be recommended for surgery lasting 90–150 min. This could be a safe and cheap alternative to extradural catheter placement for surgical procedures of intermediate duration. Clonidine has some advantages over fentanyl, as it does not produce clinically significant side effects. Indeed, undesirable side effects such as vomiting and transient oxygen desaturation were observed only in children who received extradural fentanyl. Therefore, clonidine may be the drug of choice to prolong duration of caudal anaesthesia provided by a single injection in children.

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Double-blind comparison of extradural block with three bupivacaine–ketamine mixtures in knee arthroplasty

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Summary

We have compared 0.5% bupivacaine 75 mg (group A; *n*=15) with three 0.5% bupivacaine 75 mg–ketamine mixtures for extradural block in 59 ASA I–III patients undergoing total knee replacement in a randomized, double-blind study. The following doses of preservative-free 1% ketamine were used: 0.3 mg kg^{-1} (group B: *n*=14); 0.5 mg kg^{-1} (group C: *n*=5); and 0.67 mg kg^{-1} (group D: *n*=15). Level of sensory block, degree of motor weakness and sedation scores were recorded before and after operation. Duration of postoperative analgesia was also noted. There was no difference between groups in median maximum level of sensory block (group A: T4 (range T10–T2); group B: T4 (T10–T2); group C: T4 (T8–T2); and group D: T3 (T8–C3)) or in the degree of motor block. Thirty-three of the 44 patients who received ketamine showed signs of systemic absorption (blurred vision, sedation) within 10 min of injection. There was no significant difference between groups in median duration of analgesia (group A: 240 (range 115–340) min; group B: 198 (97–460) min; group C: 150 (122–448) min; and group D: 210 (130–390) min). No patient suffered any adverse psychomimetic effects. We conclude that at the doses used, addition of ketamine to extradural bupivacaine did not improve extradural block in adult patients undergoing total knee replacement. (*Br. J. Anaesth.* 1998; **80**: 299–301)

Keywords. analgesic techniques, extradural; anaesthetics local, bupivacaive; anaesthetics i.v., ketamine, analgesia, postoperative; surgery, orthopaedic

Total knee replacement surgery is associated with significant postoperative pain.[1] It has been suggested that continuous neural block is of particular benefit in such cases.[2] The standard postoperative analgesic regimen in our hospital after total knee replacement is extradural infusion of 0.2% bupivacaine with fentanyl 10 µg ml^{-1}. These drugs have well known side effects, bupivacaine being associated with cardiovascular instability, and fentanyl causing respiratory depression, pruritis, nausea and vomiting. Furthermore, knee replacement surgery is usually performed in elderly patients who frequently have intercurrent diseases and are already prone to complications.

Given alone, extradural ketamine has a less pronounced analgesic action than opioids.[3] However, when combined with bupivacaine it has been shown to reduce the onset time of extradural anaesthesia, increase the height of sensory block[4] and increase the duration of caudal anaesthesia in children,[5] without any of the side effects associated with opioids.[6] If these advantages are also present in adults undergoing total knee replacement, ketamine may offer the possibility of good postoperative analgesia without the use of extradural opioids, and possibly with lower total doses of bupivacaine than are currently necessary.

We have studied the effect of adding three different doses of ketamine to 0.5% bupivacaine for extradural anaesthesia and analgesia in patients undergoing knee replacement surgery.

Patients and methods

After obtaining approval from the local Ethics Committee and written, informed consent, we studied 60 ASA I–III patients, weighing 80 kg or less, undergoing total knee replacement. The use of a 100-mm visual analogue scale (VAS) for pain scores (where 0 mm=no pain and 100 mm=worst pain imaginable) was explained at the preoperative visit. All patients were premedicated with temazepam 10 mg, 2 h before anaesthesia.

An i.v. infusion of Dextran 70 in 0.9% saline 500 ml was commenced in the anaesthetic room at a rate of 500 ml h^{-1}. An extradural catheter was sited at the L3–4 or L2–3 interspace using a 16-gauge Tuohy needle and an 18-gauge multi-hole catheter. All extradurals were performed by the same anaesthetist. After a negative test dose of 0.5% bupivacaine 2 ml, patients were allocated randomly to receive one of four extradural anaesthetic regimens: group A received 0.75% bupivacaine 10 ml; group B, 0.75% bupivacaine 10 ml with ketamine 0.3 mg kg^{-1}; group C, 0.75% bupivacaine 10 ml with ketamine 0.5 mg kg^{-1}; and group D, 0.75% bupivacaine 10 ml with ketamine 0.67 mg kg^{-1}. Preservative-free ketamine 10 mg ml^{-1} (Ketalar) was used in all cases. The total volume of injectate in each group was made up to 15 ml with 0.9% saline, giving each a bupivacaine concentration of 5 mg ml^{-1}. The patient and observer were unaware of the treatment allocation.

Heart rate, arterial pressure and peripheral oxygen saturation were monitored for the duration of the study. The height of sensory block (loss of sensation to cold using ethyl chloride spray), degree

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Table 1 Patient characteristics (mean (SD or range) or number) in the four groups (group A: 0.5% bupivacaine 75 mg; group B: 0.5% bupivacaine 75 mg with ketamine 0.3 mg kg^{-1}; group C: 0.5% bupivacaine 75 mg with ketamine 0.5 mg kg^{-1}; group D: 0.5% bupivacaine 75 mg with ketamine 0.67 mg kg^{-1})

	Group A	Group B	Group C	Group D
Sex (M/F)	12/3	9/5	12/3	12/3
Age (yr)	70 (57–79)	69 (59–77)	72 (58–82)	74 (61–86)
Weight (kg)	71 (6.2)	71 (8.1)	68 (5.3)	66 (8.6)
Height (cm)	159 (8.5)	161 (7.2)	159 (9.2)	157 (6.4)

Table 2 Numbers of patients with side effects during the 20 min after extradural injection in the four groups (group A: 0.5% bupivacaine 75 mg; group B: 0.5% bupivacaine 75 mg with ketamine 0.3 mg kg^{-1}; group C: 0.5% bupivacaine 75 mg with ketamine 0.5 mg kg^{-1}; group D: 0.5% bupivacaine 75 mg with ketamine 0.67 mg kg^{-1}). $^{***}P < 0.0001$

	Group A (n=15)	Group B (n=14)	Group C (n=15)	Group D (n=15)
Pain on injection	1	3	1	5
Hypotension	2	3	5	4
Sedation	0	7^{***}	12^{***}	14^{***}

of motor block (modified Bromage scale[7]) and sedation score (using existing hospital procedure: 1=drowsy, 2=asleep but rousable, 3=unrousable) were recorded at 2, 5, 10, 15 and 20 min after extradural injection.

General anaesthesia was induced 20 min after extradural injection with propofol and maintained with isoflurane and nitrous oxide in oxygen. Patients breathed spontaneously via a laryngeal mask airway unless contraindicated, in which case they received atracurium 0.5 mg kg^{-1} to facilitate tracheal intubation and positive pressure ventilation.

After operation the same observations, together with pain scores (using the 100-mm VAS) were recorded on waking, at 120, 150 and 180 min after extradural injection, and hourly thereafter.

Hypotension (decrease in systolic blood pressure of 30% or more from the preoperative value) was treated with bolus doses of ephedrine 5 mg i.v.

As soon as patients recorded a pain score of 30 mm or greater, the time was noted, the study was deemed to be complete and rescue analgesia was given (bolus dose of 0.2% bupivacaine with fentanyl 10 μg ml^{-1} extradurally followed by continuous infusion of the same solution). The time interval from extradural injection until this point was taken as the duration of analgesia.

Table 3 Maximum height of sensory block after injection and duration of analgesia (median (range)) in the four groups (group A: 0.5% bupivacaine 75 mg; group B: 0.5% bupivacaine 75 mg with ketamine 0.3 mg kg^{-1}; group C: 0.5% bupivacaine 75 mg with ketamine 0.5 mg kg^{-1}; group D: 0.5% bupivacaine 75 mg with ketamine 0.67 mg kg^{-1}). T= time of extradural injection. No significant differences between groups

	Group A (n=15)	Group B (n=14)	Group C (n=15)	Group D (n=15)
Height at T + 2 min	L3 (S1–T12)	L3 (L5–T9)	L3 (L3–T10)	L3 (L4–T6)
Height at T + 5 min	T11 (L5–T5)	T12 (L4–T4)	L1 (L5–T6)	T10 (L4–T3)
Height at T + 10 min	T8 (L5–T3)	T8 (T12–T3)	T8 (L3–T3)	T5 (L1–C4)
Height at T + 15 min	T5 (T10–T2)	T4 (T9–T2)	T4 (T9–T2)	T4 (T8–C3)
Height at T + 20 min	T4 (T10–T2)	T4 (T10–T2)	T4 (T8–T2)	T3 (T8–C3)
Duration (min)	240 (115–340)	198 (97–460)	150 (122–448)	210 (130–390)

All patients were visited 48–72 h after surgery and were questioned on the possible occurrence of dreams, hallucinations or any other psychomimetic effects of ketamine.

Data were analysed using ANOVA, chi-square and Kruskal–Wallis tests as appropriate. The study was calculated to have 80% power to detect an increase in duration of analgesia of 100%. $P<0.05$ was considered to be statistically significant.

Results

Patient characteristics are shown in table 1. One patient was withdrawn from the study because of inadvertent dural puncture.

There was no significant difference between groups in the number of patients who complained of pain on injection of the study medication, or in the number who developed hypotension within 20 min of injection. No patients became hypertensive or developed tachycardia during the study. However, compared with the control group (group A) the ketamine group had a higher incidence of sedation (table 2). In all cases, this became apparent within 10 min of injection. One patient had a sedation score of 2 (asleep but rousable), while all others scored 1 (drowsy).

There was no significant difference between groups in the rate of onset of sensory block or maximum height of block at 20 min (table 3). All patients were pain-free on waking (VAS pain score=0). When they first experienced pain, this was of sudden onset and severe, with all patients recording pain scores of greater than 30 mm. There was no significant difference in median duration of analgesia between groups (table 3). There was no difference in the degree of motor block between groups. No patient experienced hallucinations or other psychomimetic effects in the postoperative period.

Discussion

We were unable to demonstrate any increase in the rate of onset or maximum height of sensory block, or any increase in duration of analgesia resulting from the combinations of ketamine and bupivacaine. There was no significant difference in the incidence of hypotension between groups. Nine patients who were given ketamine (and one who was not) described discomfort during injection, but this was transient and not severe enough to stop the injection. The majority of patients who received ketamine reported blurred vision and drowsiness within 10 min of injection. None described this as an unpleasant sensation, and there were no postoperative sequelae.

The patients were similar in age, sex, height and weight. All had the same operative procedure, and all were cared for in the same high dependency unit after operation. There was a wide range of durations of analgesia recorded in all groups, although this does not appear to differ from other studies involving extradural anaesthesia, and probably reflects the unpredictability of spread of drugs in the extradural space. In our study, the shortest durations of analgesia were caused by regression of the block in a cephalad direction, with the upper level of the block persisting in the thoracic dermatomes.

When given extradurally or intrathecally, single boluses of preservative-free ketamine have been shown to be devoid of neurotoxic effects in animal studies.[8–11] Repeated intrathecal injections for 14 consecutive days caused no changes on light or electron microscopy of spinal cord biopsies,[12] and no neurological sequelae have been reported following the use of 1% ketamine in humans.[5]

Ketamine is a non-competitive antagonist at glutamate *N*-methyl-D-aspartate (NMDA) receptors; it inhibits the facilitated state of spinal processing caused by repetitive–persistent small afferent (C-fibre) input ("wind-up") and long-term potentiation of pain transmission.[13] Other suggested modes of action include: binding to opioid receptors[14]; local anaesthetic activity[15]; and effects on cholinergic, adrenergic and serotonergic neurotransmission.[16] It has been shown recently to potentiate the effect of extradural morphine.[17] Some authors have found that when given alone, extradural ketamine is a safe and effective drug for postoperative analgesia[18] while others have not found it to be adequate.[19] Concern has been expressed at the possibility of psychomimetic side effects, particularly when higher doses are used. These can be treated with benzodiazepines.[15] Our patients were all premedicated with temazepam. This, together with induction of general anaesthesia 20 min after injection, may have prevented these effects in our study.

Ketamine is highly lipid soluble, rapidly absorbed from the extradural space into CSF and plasma, and has a longer plasma half-life after extradural administration than if given i.v.[20] The incidence of sedation observed in our patients suggests rapid and extensive intravascular absorption of the drug from the lumbar extradural space.

Our findings do not support those of Cook and colleagues,[5] who used caudal injections for postoperative analgesia in children undergoing relatively minor surgery; their technique may result in more predictable spread of injectate. Their injections were performed after induction of general anaesthesia and so the extent of systemic absorption is uncertain; absorption of solution may be less rapid from the caudal space. In addition, Cook and colleagues used 0.25% bupivacaine; any synergistic effect of ketamine may be masked by the higher concentration (0.5%) used in our study in knee replacement surgery.

It has been shown that drug binding to NMDA receptors occurs relatively slowly,[21] and perhaps a single bolus injection provides inadequate exposure of the drug to the receptor for maximal effect. A continuous infusion may prove more effective.

We conclude that the addition of ketamine, in the doses used, to a single bolus injection of 0.5% bupivacaine had no effect on the quality or duration of extradural analgesia after knee replacement surgery.

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Glycogen depletion and lactate accumulation in human intercostal muscles after administration of succinylcholine

M. Mizuno and N. H. Secher

Summary

I.m. glycogen content, lactate concentration and staining intensity for glycogen in slow- (ST) and fast-twitch (FTa and FTb) fibres were determined in the external and internal intercostal muscles after thoracotomy. Thirteen patients received a precurarizing dose of a non-depolarizing neuromuscular blocking agent followed by the depolarizing agent, succinylcholine, to facilitate intubation of the trachea (succinylcholine group). Nine patients received pancuronium or gallamine (control group). There were no significant differences in ventilatory functional capacity between the two groups. In the external intercostal muscles, lower i.m. glycogen content was observed in the succinylcholine compared with the control group ($P < 0.05$). I.m. glycogen was depleted from the FT fibres and in particular from FTb fibres, while little depletion was noted in ST fibres. In both the external and internal intercostal muscles, a higher lactate concentration was observed in the succinylcholine than in the control group ($P < 0.05$). The results indicate that the use of succinylcholine for tracheal intubation stimulated breakdown of i.m. glycogen, particularly in fast-twitch muscle fibres, and caused accumulation of lactate in intercostal muscles. (*Br. J. Anaesth.* 1998; **80**: 302–307)

Keywords: metabolism, glycogen; metabolism, lactate; muscle skeletal, metabolism; neuromuscular block, pancuronium; neuromuscular block, succinylcholine

Depolarizing or non-depolarizing neuromuscular blocking agents can be used to facilitate intubation of the trachea. After administration of a depolarizing agent, plasma potassium concentration increases.[1–3] The efflux of intracellular potassium induced by the depolarizing agent may be caused by muscle fasciculations at the onset of neuromuscular block.[4] Even after pretreatment with a non-depolarizing agent such as tubocurarine, pancuronium or gallamine, followed by succinylcholine, plasma potassium concentration is higher than after the use of a non-depolarizing agent alone.[1–3] Fasciculation of ventilatory and other skeletal muscles is observed after combined administration of a non-depolarizing and depolarizing agent.[5–7]

In a preliminary report, we noted a high lactate concentration and a low glycogen content in the intercostal muscles of surgical patients in whom the depolarizing agent, succinylcholine, was used to facilitate intubation of the trachea.[8] This occurred even though a precurarizing dose of a non-depolarizing agent was used. No control group was available, but the difference was marked compared with reported values from spontaneously breathing patients.[9] These results indicate that muscle fasciculations induced by succinylcholine cause i.m. metabolic changes similar to those observed in limb skeletal muscles during exercise. A breakdown of i.m. glycogen and accumulation of lactate occurs in proportion to the intensity and duration of exercise[10 11]; it also depends on the type of muscle fibres recruited.[12]

Human skeletal muscles,[13] including ventilatory muscles,[14] consist of two major fibre types: slow- (ST or type I) and fast-twitch (FT or type II), with FT fibre subgroups (FTa and FTb). ST fibres contract more slowly and fatigue less during repetitive contractions compared with FTb fibres.[15] ST fibres have higher mitochondrial and lower glycolytic enzyme activities than FTb fibres. Fatigue characteristics and metabolic properties of FTa fibres resemble those of ST fibres, but they contract at a speed comparable with FTb fibres.

Histochemical evaluation of muscle fibre types and estimation of i.m. glycogen in individual muscle fibres allows investigation of glycogen depletion in specific types of muscle fibres.[16–18] We have evaluated the effect of a precurarizing dose of a non-depolarizing agent followed by succinylcholine on glycogen content and lactate concentration in external and internal intercostal muscles of patients undergoing thoracotomy. Histochemical evaluation of staining intensity for i.m. glycogen in ST and FT fibres was performed and data were compared with those obtained from similar biopsies of patients who received only a non-depolarizing agent.

Patients and methods

We studied 22 patients with no history of neuromuscular disease who fasted overnight and underwent thoracotomy for benign ($n = 6$) or malignant ($n = 16$) pulmonary disease (table 1). In order to obtain data

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Table 1 Physical and ventilatory characteristics, and glycogen content and lactate concentration in external and internal intercostal muscles for two groups of patients undergoing thoracotomy with and without the use of succinylcholine (mean (SD or range) or number). FEV$_1$=forced expiratory volume in 1 s; FVC=forced vital capacity; MBC=maximal breathing capacity. *$P<0.05$ between groups

	Succinylcholine group	Control group
n	13	9
Sex (F/M)	2/11	2/7
Tumour (benign/malignant)	2/11	4/5
Age (yr)	56 (35–71)	54 (28–75)
Height (cm)	175 (9)	171 (6)
Weight (kg)	75 (13)	70 (18)
FEV$_1$ (litre s^{-1})	2.4 (0.7)	2.0 (0.5)
FVC (litre)	3.7 (0.7)	3.4 (0.6)
MBC (litre min^{-1})	94 (24)	98 (15)
Glycogen (μmol g^{-1} dry wt)		
External	233.0 (60.7)*	305.8 (60.0)
Internal	298.7 (148.3)	315.8 (80.2)
Lactate (μmol g^{-1} dry wt)		
External	23.6 (10.7)*	6.5 (3.1)
Internal	24.8 (11.2)*	11.4 (3.5)

using two non-depolarizing neuromuscular blocking agents, in four patients intubation of the trachea was facilitated by a precurarizing dose of pancuronium 1 mg, and in nine patients, gallamine 20 mg. A mean dose of succinylcholine 130 mg (range 100–150 mg) was then administered (succinylcholine group). In the other nine patients, pancuronium 8 mg ($n = 1$) or gallamine 160 mg (120–240 mg) ($n = 8$) was used for tracheal intubation (control group). Patients were allocated randomly to receive succinylcholine. The study was approved by the local Ethics Committee. In all patients, induction of anaesthesia comprised fentanyl 3 μg kg^{-1}, midazolam 0.07 mg kg^{-1} and thiopental 3 mg kg^{-1}, and was maintained with 70% nitrous oxide in oxygen. We did not use halothane or isoflurane as these agents may influence glycogen depletion and lactate accumulation in skeletal muscle after the use of succinylcholine because of "desensitization" of nicotinic cholinergic receptors.[19]

BIOPSY SAMPLING

Surgical biopsies of the external and internal intercostal muscles were obtained from the fourth to the seventh intercostal space in the mid-axillary line. The muscle sample was dissected immediately into two parts. One piece for biochemical analysis was frozen directly in liquid nitrogen. The remaining portion for histochemical analysis was mounted in an embedding medium (OCT Compound, Miels Tissue-Tek), frozen in isopentane and cooled to freezing point by liquid nitrogen. These samples were stored at −80 °C until analyses were performed. Biochemical and histochemical analyses of muscle biopsies were performed without knowledge of the drug(s) used for tracheal intubation.

BIOCHEMISTRY

The muscle samples for quantitative determination of glycogen content and lactate concentration were freeze-dried in a thermoelectric freeze-dryer (Hetosic CD 52) for 48 h at −50 °C at a pressure of 0.01 Torr. Thereafter, each muscle sample was dissected under a microscope to remove blood, fat and connective tissue in a room where the temperature (20 °C) and humidity (<30%) were controlled. The dissected fibre fragments of 1.5 (0.5–3.0) mg dry weight for glycogen and 1.3 (0.5–2.7) mg dry weight for lactate were hydrolysed with HCl 1 mol litre^{-1}. Samples for glycogen were hydrolysed further at 100 °C for 2 h; glycogen was analysed as glucose residues. Glucose and lactate concentrations were measured fluorometrically.[20] The coefficients of variance of double determinations of glycogen content and lactate concentrations were 1.8% and 5.6%, respectively.

HISTOCHEMISTRY

The frozen muscle sample was replaced in a Cryo-cut Cryostat Microtome (American Optical). In order to evaluate the relative glycogen content of individual muscle fibres, one transverse section (16 μm thick) was cut at −20 °C and stained for glycogen by the periodic acid–Schiff (PAS) reaction.[21] Under light microscopy the staining intensity of the fibres was rated as "dark", "moderate", "light" or "negative" and ranked 3 to 0, respectively.[17 18] The proportion of the four-rated intensities and mean staining intensity as an average of ranked values were determined for each muscle biopsy. The rating was performed on 392 (287–539) fibres in each muscle biopsy.

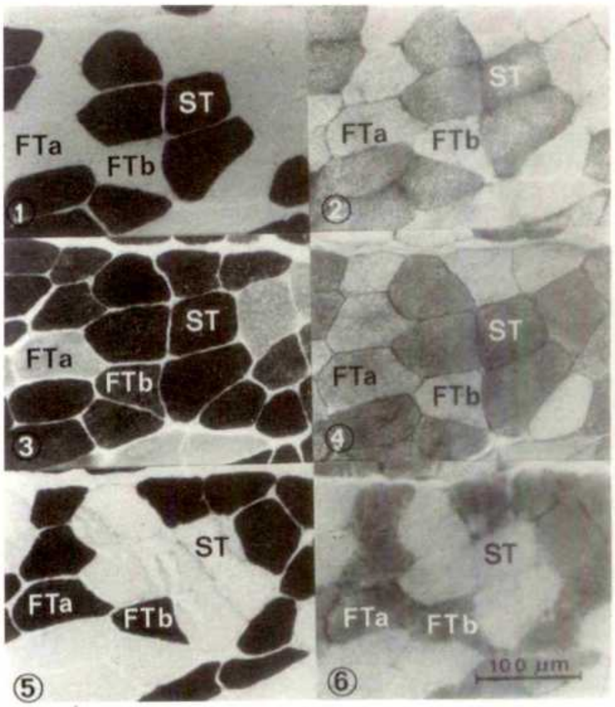

Figure 1 Photomicrographs of serial transverse sections from external intercostal muscles obtained after the use of succinylcholine. Staining for myofibrillar ATPase after preincubation at pH 4.3 (1), 4.6 (3) and 10.3 (5); for reduced nicotinamide adenine dinucleotide tetrazolium (2); for glycogen (4); and for alpha-glycerophosphate dehydrogenase (6). In the left panels (1, 3, 5) it is possible to identify ST, FTa and FTb fibres. ST fibres are stained dark in (1), whereas FTa and FTb fibres are stained dark in (5). In (3), FTa fibres are stained lighter than FTb fibres. ST and FT fibres are also identified in staining for a mitochondrial enzyme (2) and for a glycolytic enzyme (6). The level of glycogen content in individual fibres is classified in (4). The staining intensity is rated as dark for ST fibres, moderate for FTa fibres and either light or negative for FTb fibres.

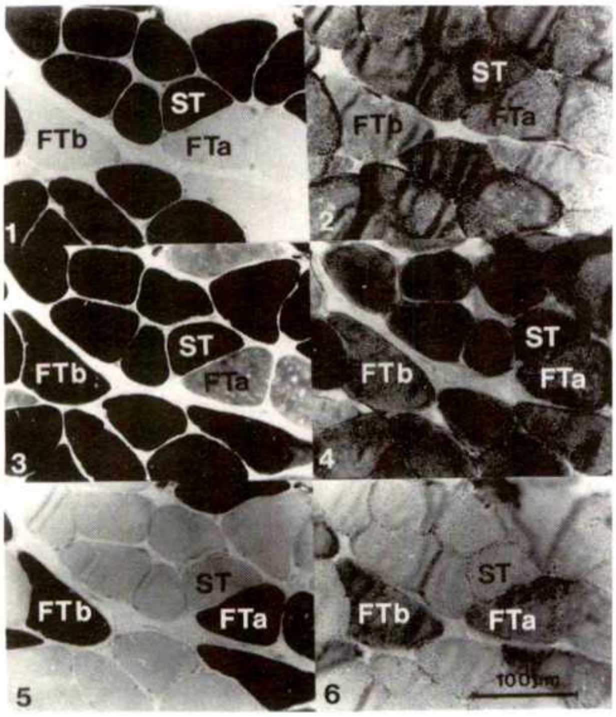

Figure 2 Photomicrographs of serial transverse sections from external intercostal muscles obtained after intubation of the trachea without the use of succinylcholine. Staining for myofibrillar ATPase after preincubation at pH 4.3 (1), 4.6 (3) and 10.3 (5); for reduced nicotinamide adenine dinucleotide tetrazolium (2); for glycogen (4); and for alpha-glycerophosphate dehydrogenase (6) (see legend to fig. 1). Note the intense glycogen staining in all three fibre types (4).

Five serial transverse sections (10 μm thick) were also cut and incubated for myofibrillar adenosine triphosphatase (ATPase) reaction at pH 9.4,[22] after preincubation at pH 4.3, 4.6 or 10.3.[23] The remaining two sections were incubated with reduced nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR)[24] or alpha-glycerophosphate dehydrogenase (α-GPD)[25] as markers for oxidative and glycolytic potentials, respectively. These sections were used to evaluate coupling between contractile and metabolic characteristics of individual fibres. Based on myofibrillar ATPase staining, individual fibres were classified under light microscopy as ST, FTa, FTb or unidentified.[26] The relative occurrence of each fibre type was determined from 544 (187–937) fibres in each biopsy. Unidentified fibres (range 0.3–1.5 %) were not included in the analysis for histochemical evaluation of i.m. glycogen.

STATISTICAL ANALYSIS

Values are expressed as mean (SD). Glycogen content, lactate concentration and glycogen staining were compared between the two groups using the Mann–Whitney *U* test.[27] Spearman's coefficient of rank correlation was use to evaluate interdependencies. A level of 5% was considered significant for two-tailed tests.

Results

There was no significant difference in patient characteristics or ventilatory functional capacity between the two groups (table 1). Mean time from the start of anaesthesia to biopsy sampling was 35 min (range 20–55 min); there was no difference between the two groups.

GLYCOGEN AND LACTATE CONCENTRATION

In the external intercostal muscle, the succinylcholine group showed a 20% lower glycogen content and a four-fold higher lactate concentration than the control group (table 1). Similarly, lactate concentration in the internal intercostal muscle was two-fold higher in the succinylcholine than in the control group, while no significant difference in i.m. glycogen content was observed. A significant correlation could not be demonstrated between lactate concentration and glycogen content or between lactate concentration determined in external or internal intercostal muscles and time of sampling of the biopsy. For both groups, comparison between external and internal intercostal muscles revealed no significant difference in glycogen content or lactate concentration. There was no difference in muscle biochemistry between patients with benign or malignant disease.

GLYCOGEN DISTRIBUTION IN MUSCLE FIBRE TYPES

The relative occurrence of ST, FTa and FTb fibres was 62 (9), 17 (9) and 21 (10) % for external intercostal muscles and 59 (18), 39 (15) and 2 (3) % for internal intercostal muscles (ns between groups).

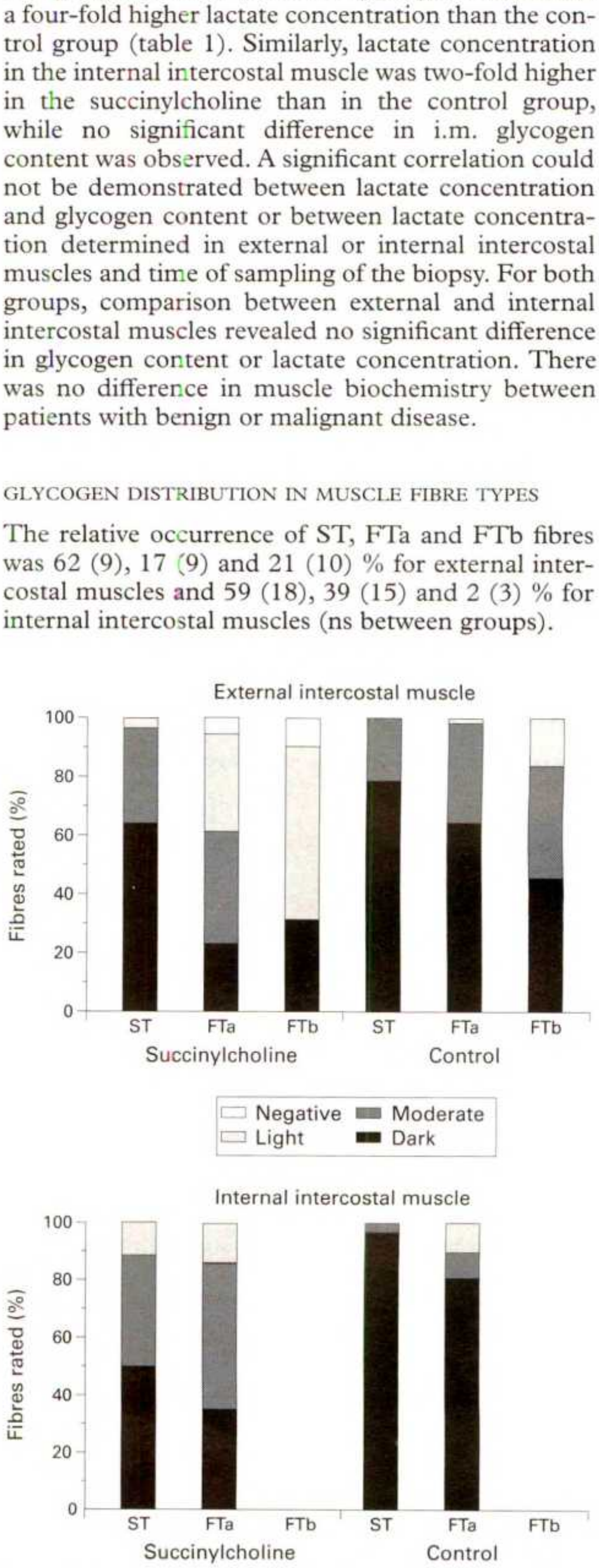

Figure 3 Glycogen depletion pattern in external and internal intercostal muscles after intubation of the trachea with (succinylcholine) or without (control) the use of succinylcholine. Y-axis shows the percentage of fibres rated. Based on the staining intensity for glycogen, individual muscle fibres are ranked as dark, moderate, light or negative ((4) in figs 1 and 2).

For external intercostal muscles, staining intensity for glycogen of ST fibres was similar in the succinylcholine and control groups (dark 65 (21) *vs* 78 (20) %; moderate 32 (14) *vs* 21 (19) %), while FTa fibres stained weaker in the succinylcholine than in the control group (dark 23 (25) *vs* 64 (28) %; moderate 38 (20) *vs* 34 (24) %; light 33 (22) *vs* 2 (7) %; negative 6 (1) *vs* 0 (0) %) (figs 1–3). In particular, FTb fibres were stained the weakest (dark 0 (0) *vs* 45 (35) %; moderate 31 (26) *vs* 38 (23) %; light 60 (23) *vs* 17 (25) %; negative 9 (13) *vs* 0 (0) %). Mean staining intensity for glycogen in FT fibres was lowest in the succinylcholine group (FTa 1.8 (0.6) *vs* 2.6 (0.3) %; FTb 1.2 (0.3) *vs* 2.3 (0.6) % ($P < 0.01$)), while a similar value was obtained for ST fibres (2.6 (0.3) *vs* 2.7 (0.3) %).

In the internal intercostal muscles, for which ST and FTa fibres were mainly identified, both fibre types were stained more weakly in the succinylcholine than in the control group (ST: dark 50 (33) *vs* 96 (8) %; moderate 39 (22) *vs* 4 (8) %; light 11 (14) *vs* 0 (0) %; FTa: dark 34 (33) *vs* 89 (23) %; moderate 52 (26) *vs* 11 (21) %; light 14 (19) *vs* 11 (21) %). Thus mean staining intensity for glycogen in both fibre types was also low in the succinylcholine group (ST 2.3 (0.5) *vs* 3.0 (0.1) %; FTa 1.9 (0.8) *vs* 2.9 (0.3) %).

ST fibres were stained darker for NADH-TR activity than FT fibres in both muscles, whereas the opposite was seen for α-GPD (figs 1 and 2). There was no difference in staining intensity for these enzyme activities between the two groups.

Discussion

We have demonstrated that the use of succinylcholine for intubation of the trachea in patients undergoing thoracotomy caused substantial breakdown of i.m. glycogen in external intercostal muscles and an increase in lactate concentration in both external and internal intercostal muscles. This was the case although a precurarizing dose of a non-depolarizing agent (either pancuronium or gallamine) was used before succinylcholine. Biochemical changes are more likely to be produced if succinylcholine alone has been administered, as the level of muscle fasciculation[5 7] and increase in plasma potassium[5] are larger without pretreatment with non-depolarizing agents. The degree of glycogen depletion in individual muscle fibres was evaluated in histochemical transverse sections stained by the PAS technique. The results indicated that i.m. glycogen in FT fibres, particularly in FTb fibres, was more depleted than in ST fibres for both external and internal intercostal muscles. The predominant effect of succinylcholine on FT fibres in this study agrees with results from human limb skeletal muscles.[28 29]

GLYCOGEN AND LACTATE CONCENTRATION

Evaluation of glycogen depletion was based on the assumption that, before operation, the level of glycogen was similar in the two groups of patients. Similar i.m. glycogen content for external and internal intercostal muscles (250 and 309 μmol g^{-1} dry weight, respectively) was reported in biopsies obtained from patients with chronic obstructive pulmonary disease during thoracotomy after administration of both depolarizing and non-depolarizing neuromuscular blocking agents.[30] In contrast, approximately half of that value (170 μmol g^{-1} dry weight) was observed in biopsies obtained from the external intercostal muscle of healthy controls under local anaesthesia during spontaneous breathing.[9] Thus glycogen content of intercostal muscles may be affected by the ventilatory capacity of the patient. It is unlikely, however, that the lower glycogen content and higher lactate concentration observed in the succinylcholine group were caused by a difference in ventilatory capacity, as FEV_1, FVC and MBC were similar in the two groups. Further, in this study, approximately 70% of subjects had malignant disease. This is in accordance with a previous observation[30] that malignant disease does not appear to affect i.m. glycogen content and lactate concentration of external and internal intercostal muscles.

In the control group, lactate concentrations in external (7 μmol g^{-1} dry weight) and internal (11 μmol g^{-1} dry weight) intercostal muscles were similar to reported values (7–12 μmol g^{-1} dry weight), while those observed in the succinylcholine group (25 μmol g^{-1} dry weight) were higher.[9] A similar value to that determined in the control group (10 μmol g^{-1} dry weight) was also reported in biopsies obtained from both external and internal intercostal muscles after the use of succinylcholine.[30] Why lactate concentration was lower in their study compared with the succinylcholine group reported here is not obvious. One explanation could be a shorter time between the use of succinylcholine and biopsy in this study (35 min) compared with a previous study, although the time was not given.[30] Alternatively, a smaller precurarizing dose of a non-depolarizing agent could have been administered in this study. Lactate concentration determined in thigh muscles 30 min after intense exercise[31 32] corresponds to that obtained in our succinylcholine group (25 μmol g^{-1} dry weight). During recovery from extremely heavy bicycling, muscle lactate concentration reaches approximately 80 μmol g^{-1} dry weight.[32]

FIBRE TYPE SPECIFICITY OF NEUROMUSCULAR BLOCKING AGENTS

A preferential effect of succinylcholine on FT fibres was indicated in this study. This finding is supported by results from animal experiments, demonstrating that the neuromuscular blocking agent decamethonium[33 34] and succinylcholine[35] have a preference for muscles dominated by FT fibres. In contrast, the non-depolarizing neuromuscular blocking agent, tubocurarine, has a preference for muscles dominated by ST fibres.[33 34] Similar findings are available from human extremity skeletal muscles with respect to the isometric mechanogram and force during maximal voluntary contraction[36 37]; endurance time[38] and electromyographic activity during a sustained contraction[28]; glycogen depletion pattern during cycling[39]; and ^{31}P-NMR detected energy metabolism during rhythmic forearm exercise.[29]

Coupling between the pattern of i.m. glycogen depletion and involvement of a specific type of muscle fibre is demonstrated during low intensity exercise with selective glycogen depletion from ST fibres, while high intensity exercise results in depletion of glycogen from FT fibres,[17 18 29] and in particular from FTb fibres.[40] However, there may not be a direct link between the pattern of i.m. glycogen depletion and involvement of specific muscle fibres during muscle fasciculations after the use of succinylcholine. Quantitative analyses of single human muscle fibres reveal that FT fibres have larger glycolytic potentials than ST fibres. In addition, a subgroup of FT fibres (FTb fibres) show the largest potentials.[41] Furthermore, FT fibres use more ATP and thereby deplete a larger amount of glycogen than ST fibres during repeated electrical stimulation-induced contractions.[42] Thus there is a metabolic bias to support the preferential effect of succinylcholine on FT and, in particular, on FTb fibres. Therefore, we conclude that after administration of succinylcholine, depletion of glycogen and accumulation of lactate take place predominately in the fast-twitch fibres of human skeletal muscles.

What would be the clinical implications of selective glycogen depletion and accumulation of lactate in intercostal muscles after the use of succinylcholine? When the glycogen concentration in exercising muscles during bicycling becomes significantly low (<80 μmol g^{-1} dry weight), it is associated with reduced performance.[17] However, the reduction in i.m. glycogen in external intercostal muscle is less, and is not therefore expected to affect ventilation. Equally, the increase in muscle lactate, approximately 30 min after the use of succinylcholine, may not influence patients by the time the operation is completed, as the level of muscle lactate would by then have returned to resting levels.[31 32] However, with the combined use of depolarizing and non-depolarizing neuromuscular blocking agents during surgery, postoperative ventilatory function may be impaired by the combined effects of persistent neuromuscular block of, in particular, ST fibres by the non-depolarizing agent and weakness caused by the development of fatigue in glycogen-depleted FT fibres by the depolarizing agent.

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Augmentation of the neuromuscular blocking effects of cisatracurium during desflurane, sevoflurane, isoflurane or total i.v. anaesthesia

H. Wulf, M. Kahl and T. Ledowski

Summary

We have evaluated the enhancement of cisatracurium-induced neuromuscular block by potent inhalation anaesthetic agents, by constructing dose–effect curves for cisatracurium in 84 patients during anaesthesia with 1.5 MAC (70% nitrous oxide) desflurane, sevoflurane, isoflurane or total i.v. anaesthesia (TIVA). Acceleromyography (TOF-Guard) and train-of-four (TOF) stimulation of the ulnar nerve were used (2 Hz every 12 s). Cisatracurium was administered in increments of 15 μg kg^{-1} until depression of T1/T0 >95% was reached. ANOVA was used for statistical analysis ($\alpha = 0.05$, $\beta = 0.2$). Depression of T1/T0 during potent inhalation anaesthesia was enhanced compared with TIVA. ED_{50} and ED_{95} values of cisatracurium were 15 (SD 5) and 34 (10) μg kg^{-1} for desflurane; 15 (4) and 32 (7) μg kg^{-1} for sevoflurane; and 15 (5) and 33 (9) μg kg^{-1} for isoflurane. These were significantly lower than the values for TIVA (21 (4) and 51 (13) μg kg^{-1}) ($P < 0.01$ in each case). After equi-effective dosing, times to T1/T0 = 25% were similar in all groups (19 (7), 19 (5), 20 (5) *vs* 16 (4) min). Recovery $\text{index}_{25\text{–}75\%}$ and time to a TOF ration of 0.70 were prolonged significantly by desflurane and sevoflurane compared with TIVA (18 (5), 19 (8) *vs* 12 (4) min and 43 (11), 44 (10) *vs* 35 (5) min, respectively), whereas the difference was not significant for isoflurane (14 (6) and 41 (7) min). (*Br. J. Anaesth.* 1998; **80**: 308–312)

Keywords: neuromuscular block, cisatracurium; neuromuscular block, measurement of response; anaesthetics i.v.; anaesthetics volatile, desflurane; anaesthetics volatile, isoflurane; anaesthetics volatile, sevoflurane

The neuromuscular blocking effect of neuromuscular blocking agents may be enhanced by potent inhalation anaesthetics.[1 2] The magnitude of this effect on the dose–response curve has not been investigated for the recently introduced agent, cisatracurium. This isomer of atracurium is a non-depolarizing neuromuscular blocking agent of the benzylisoquinoline type with fewer side effects than its predecessor, atracurium. The inhalation agents, sevoflurane and desflurane, have a low blood-gas solubility, resulting in rapid uptake and elimination. Their physicochemical properties allow fast recovery thus making both agents suitable for day-case surgery. Underestimation of enhancement of neuromuscular block by potent inhalation agents could result in inadvertent prolongation of block. Therefore, the interaction of cisatracurium with desflurane and sevoflurane was compared with its neuromuscular blocking effects during anaesthesia with isoflurane or total i.v. anaesthesia (TIVA).

Patients and methods

The study was planned in accordance with the recommendations outlined in "Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents".[3] The time required for the first twitch (T1) to recover from 25 to 75% (recovery index) after administration of cisatracurium was mean 9.5 (SEM 1.7) min during halothane anaesthesia in children.[4] Three studies in adults during TIVA reported recovery indices (25–75% recovery of T1/T0) of 17 (SD 5), 17 (SEM 1) or 12.6 (SEM 0.6) min after a single dose of cisatracurium 100 μg kg^{-1}, while recovery time to a train-of-four (TOF) ratio of 0.7 was reported to be 66.7 (SEM 4.9) min.[4–8] If a difference of 20% in potency or recovery time is considered clinically relevant, the calculated sample size would be at least 11 (6–20) patients per group for a single comparison ($\alpha = 0.05$, $\beta = 0.2$; power 80%). As comparison of both desflurane and sevoflurane with TIVA was planned, and as some drop-outs were anticipated, a sample size of 21 patients per group was deemed appropriate.

After obtaining approval from the Ethics Committee and written informed consent, we studied 84 consecutive Caucasian male or female adults (ASA I or II) in a prospective, randomized study. Patients were undergoing minor elective extra-abdominal and extra-thoracic surgery and were free from neuromuscular and endocrine disease. Exclusion criteria were: body weight greater or less than 30% of ideal; patients younger than 18 yr or older than 65 yr; pregnancy or breast feeding; history or laboratory signs of renal (creatinine >100 μmol litre^{-1}) or hepatic (γ-GT >333 nmol·s^{-1} litre^{-1}) disease; paresis; bedridden patients; medication known to interact with non-depolarizing neuromuscular blocking agents; and allergic diathesis.

Cumulative dose–effect curves for cisatracurium were determined during anaesthesia with 1.5 MAC of desflurane (4.2 vol%), sevoflurane (1.05 vol%) or isoflurane (0.75 vol%) (adjusted for concomitant use of 70% nitrous oxide) and compared with the

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potency determined in patients during total i.v. anaesthesia (TIVA) using propofol–fentanyl. Premedication comprised a benzodiazepine orally on the evening before surgery. Anaesthesia was induced with propofol 2–2.5 mg kg^{-1} and fentanyl 100 µg i.v. in the arm opposite to that connected to the neuromuscular monitoring equipment. Inhalation anaesthetics were administered starting with 2.5–3.0 MAC and the concentration was reduced over the next few minutes to 1.5 MAC. All groups received 70% nitrous oxide in oxygen. End-tidal $P\text{CO}_2$ was adjusted to 4.3–4.7 kPa. Body temperature and skin temperature above the monitored muscle were measured and maintained above 35 °C and 32 °C, respectively, by passive warming (wrapping of the patient and arm in a cotton blanket). The arterial pressure cuff was placed on the opposite arm. Light anaesthesia or moderate hypertension (>120% of baseline) was treated initially with fentanyl 100 µg i.v. and, if necessary, by 20% increments of the end-tidal concentration of the inhalation anaesthetic or propofol infusion rate. Hypotension (<80% of baseline) was treated initially by infusion of fluids and then by decreasing by 20% end-tidal concentration of inhalation anaesthetic or propofol infusion rate.

NEUROMUSCULAR MONITORING

The left arm was used for neuromuscular monitoring and was attached to a special arm board (Armboard TOF-Guard, Biometer Int., Odense, Denmark). Neuromuscular monitoring was performed using acceleromyography (AMG) with the piezoelectric ceramic wafer placed at the distal interphalangeal joint of the thumb (TOF-Guard, Biometer Int., Odense, Denmark). Train-of-four (TOF) stimulation of the ulnar nerve via surface stimulating electrodes placed at the wrist was used (supramaximal square wave impulses with 2 Hz, applied every 12 s, 200 µs duration). All data were stored electronically and read out into a computer program for further analysis (TOF-Guard Card Reader 1.0 for Windows, supplied by Organon Teknika, Belgium). Cisatracurium was administered when steady-state conditions were reached (stable control response of AMG for 5 min)[9] and equilibrium of inspiratory and end-tidal concentrations of potent inhalation anaesthetics had occurred, as measured by a Capnomac (Datex).[10] Cumulative increments of cisatracurium 15 µg kg^{-1} were administered repeatedly (injection time <5 s into a fast running i.v. infusion) until depression of the first twitch of at least 95% was achieved.[11] The subsequent dose was administered after at least 4 min and only if three consecutive twitches of identical amplitude were demonstrated (steady state of onset). In addition to depression of the first twitch response, the following variables of neuromuscular block were obtained: duration 25% (time after injection of the last cumulative dose until 25% recovery of T1); recovery index (time to recovery of T1 from 25% to 75%); and interval T1 (25% to a TOF ratio of 0.7). Instead of TOF 0.8 (as suggested by the GCRP guidelines[5]), TOF 0.7 was used as, following our usual clinical practice, in some patients the concentration of inhalation anaesthetic had already been reduced towards the end of operation.

In case of significant baseline shift (defined as failure of T1 to recover to 85–110% with a TOF ratio >0.8), the patient was excluded from further analysis.

CALCULATIONS AND STATISTICAL ANALYSIS

Individual dose–response curves were established by plotting the logarithm of the dose against the logit transform of depression of T1 relative to baseline (100% depression of T1 was adjusted to 99%, 0% to 1%, respectively) using linear least squares regression. After testing for deviation from parallelism, group dose–response curves were established. The ED$_{50}$ and ED$_{95}$ values of cisatracurium were calculated. Data are presented as mean (SD or range). Statistical analysis was performed by one-way ANOVA (Kruskal–Wallis test with post-test; Dunnet's multiple comparison test) using GraphPad Prism 2.0. α was set at 0.05 and β was set at 0.2 (power 80%).

Results

Patients in all groups were similar in age, weight and sex distribution (table 1). Results from six patients were excluded from further analysis (drop-outs)

Table 1 Patient characteristics (mean (SD) [range])

	Sex (M/F)	Weight (kg)	Height (cm)	Age (yr)
Desflurane	12/9	74 (13) [52–98]	174 (10) [174–192]	47 [20–64]
Isoflurane	10/9	75 (12) [54–99]	174 (9) [158–194]	46 [18–63]
Sevoflurane	17/4	76 (13) [50–100]	178 (8) [160–193]	45 [18–65]
TIVA	12/5	76 (15) [54–102]	177 (9) [162–198]	42 [20–64]

Table 2 Depression of T1/T0 after three cumulative doses of cisatracurium 15 µg kg^{-1} during desflurane, isoflurane, sevoflurane and total i.v. anaesthesia (TIVA). ED$_{50}$ and ED$_{95}$ values were calculated after logit transformation (in the 45 µg kg^{-1} column, depression was set at 100% if > 95% was already reached with cisatracurium 30 µg kg^{-1}). In nine of the 17 patients in the TIVA group, a cumulative dose of cisatracurium 60 µg kg^{-1} was given to obtain twitch depression greater than 95%. Mean effect following this dose in the TIVA group was 98 (SD 3)%. Values are mean (SD) [range]. Significant difference compared with TIVA group· * $P < 0.05$, ** $P < 0.01$

	T1/T0 (%)				
	15 µg kg^{-1}	30 µg kg^{-1}	45 µg kg^{-1}	ED$_{50}$ (µg kg^{-1})	ED$_{95}$ (µg kg^{-1})
Desflurane (n=21)	39 (25)*	89 (12)**	98 (3)**	15 (6) [6–24]*	34 (10) [16–56]**
Isoflurane (n=19)	38 (26)*	91 (10)**	98 (4)**	15 (5) [7–24]**	33 (9) [21–55]**
Sevoflurane (n=21)	38 (25)*	91 (9)**	99 (2)**	15 (4) [9–21]**	32 (7) [25–52]**
TIVA (n=17)	14 (16)	71 (18)	92 (7)	21 (4) [13–31]	51 (13) [30–74]

Table 3 Recovery from neuromuscular block during desflurane, isoflurane, sevoflurane and total i.v. anaesthesia after equi-effective doses of cisatracurium (maximal depression of T1/T0 > 95%) (mean (SD) [range]). Significant difference compared with TIVA group: * $P < 0.05$, ** $P < 0.01$

	Duration 25% (min)	Recovery index$_{25-75\%}$ (min)	TOF ratio = 0.70 (min)
Desflurane (n=21)	19 (6) [11–33]	18 (5) [12–29]**	43 (11) [28–59]*
Isoflurane (n=19)	20 (4) [13–27]	14 (6) [7–26]	41 (6) [33–54]
Sevoflurane (n=21)	19 (5) [12–30]	19 (8) [11–40]**	44 (10) [31–65]**
TIVA (n=17)	16 (4) [8–25]	12 (4) [6–20]	35 (6) [23–42]

because of significant baseline shift ($n = 5$) or reduction of the concentration of the inhalation anaesthetic to less than 1.2 MAC ($n = 1$). In two patients in the isoflurane group and in one in the sevoflurane group, the concentration of inhalation anaesthetic was reduced intermittently to 1.2 MAC during the study because of arterial hypotension. In one patient in each of the inhalation groups the concentration was increased to 1.8 MAC intermittently.

Cisatracurium in cumulative doses led to more pronounced depression of T1 when anaesthesia was maintained with desflurane, sevoflurane or isoflurane compared with the TIVA group (table 2) ($P < 0.01$). To obtain an end-point of T1 of less than 5%, the incremental dose of 15 μg kg^{-1} was administered 2.2 (0.5) (range 1–3), 2.2 (0.5) (2–4) or 2.4 (0.6) (2–4) times in the inhalation anaesthetic groups compared with 3.5 (0.7) (2–5) times in the TIVA group.

The calculated ED$_{50}$ (dose resulting in a 50% effect) and ED$_{95}$ were significantly lower during desflurane (15 (5) and 34 (10) μg kg^{-1}), sevoflurane (15 (4) and 32 (7) μg kg^{-1}) and isoflurane (15 (5) and 33 (9) μg kg^{-1}) anaesthesia compared with the TIVA group (21 (4) and 51 (13) μg kg^{-1}) ($P < 0.01$ in each case) (fig. 1). The dose–response curves were shifted to the left without a significant effect on the slopes compared with TIVA. The degree of potentiation (ratio of ED$_{50}$ during inhalation anaesthesia/ED$_{50}$ during TIVA) was 1.4 for all inhalation anaesthetics.

After equi-effective dosing (e.g. depression of T1/T0 >95%), there were no significant differences in duration 25% for the four groups (19 (7), 19 (5), 20 (5) *vs* 16 (4) min). For desflurane and sevoflurane compared with TIVA, recovery index$_{25-75\%}$ (18 (5), 19 (8) *vs* 12 (4) min) and a TOF ratio of 0.07 (43 (11), 44 (10) *vs* 35 (5) min) were prolonged significantly. There was no significant difference in these variables for isoflurane (14 (6) and 41 (7) min) (table 3).

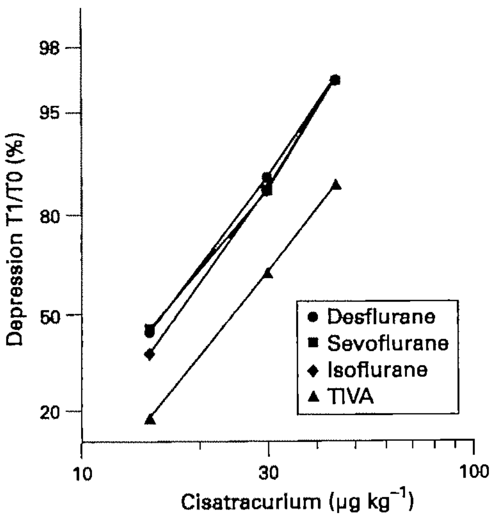

Figure 1 Log-probit plot comparing cumulative bolus dose–response curves for neuromuscular block induced by cisatracurium during desflurane, sevoflurane, isoflurane (1.5 MAC) and total i.v. anaesthesia (TIVA) (depression was set at 100% if >95% was already reached with cisatracurium 30 μg kg^{-1}).

There were no significant adverse effects attributable to the use of cisatracurium, any of the inhalation anaesthetics or TIVA in any patient.

Discussion

The aim of this study was to determine the influence of the inhalation anaesthetics, desflurane and sevoflurane, on the dose–response relationship and pharmacodynamic profile of cisatracurium. The results were compared with those obtained after total i.v. anaesthesia (TIVA). In this study the neuromuscular blocking effect of cisatracurium was enhanced by desflurane, sevoflurane and isoflurane to a similar extent.

POTENCY (AUGMENTATION OF DEPRESSION OF T1/T0)

The cumulative dose technique may underestimate the potency of neuromuscular blocking agents. However, administration of cisatracurium was standardized and the use of potent inhalation anaesthetics or TIVA was randomized; thus the cumulative pattern of cisatracurium administration would have similar effects in all groups. The aim of our study was to determine the anaesthesia-related effects of cisatracurium and not to provide absolute potency data. Nevertheless, the ED$_{95}$ obtained in the present study (51 μg kg^{-1} in the TIVA group) is in accordance with results reported by others (48 μg kg^{-1}, 53 μg kg^{-1}).[8 12]

Using a continuous infusion technique of cisatracurium, Oyos and co-workers reported (in a small number of patients; 14 in four groups) 30–40% reduction in infusion rate required to maintain approximately 95% T1/T0 suppression during enflurane–nitrous oxide and isoflurane–nitrous oxide compared with propofol–nitrous oxide or fentanyl–nitrous oxide anaesthesia.[13] Their data are similar to ours using a cumulative dosing technique during desflurane, sevoflurane and isoflurane anaesthesia. The degree of potentiation found in our study is also in accordance with that reported for other neuromuscular blocking drugs such as rocuronium (factor 1.25–1.4).[14] In theory, assuming that neuromuscular block becomes apparent at 70–75% receptor occupancy and is half maximal at 87.5% receptor occupancy, the ratio ED$_{95}$/ED$_{50}$ should be 1.95. Our results demonstrated that this holds approximately true for cisatracurium during four different anaesthetic techniques (2.26, 2.13, 2.2 and 2.4). Similar results have been obtained for rocuronium (2.06, 2.0, 1.75 and 1.92).[15]

We started our measurements approximately 10–15 min after induction of anaesthesia. Accelerometric monitoring has been shown to result in stable effects after an equilibration period of 10 min or less.[9] Inspiratory and end-tidal concentrations of each inhalation agent also indicated that steady state was approached. Diffusion of the inhaled anaesthetics into the muscle compartment is slow and requires approximately 30–45 min to approach equilibration. Recent studies indicated that a constant uptake process for desflurane and isoflurane may even continue for more than 1 h.[16] Therefore, in our study this process was probably not complete. Enhancement of neuromuscular block might still increase after more than 1 h of anaesthesia with potent inhalation agents.[17–20] Studies beyond this period are difficult to accomplish and bear little relevance to the routine clinical use of these agents.[21] Typical clinical practice is to administer the first dose of neuromuscular blocking agent soon after induction and before stable anaesthesia has been achieved. Nevertheless, because of the difference in physicochemical properties, equilibration between the muscle compartment and end-tidal concentration is faster for desflurane and sevoflurane than for isoflurane.[22 23] This phenomenon could explain the less pronounced effects of isoflurane on duration and recovery in this study.

DURATION AND RECOVERY

Duration and recovery depend on the dose of the neuromuscular blocking agent.[2 8 24] The most probable reason for the longer duration of action observed in some studies compared with our results is that cisatracurium was given in higher doses (e.g. duration 25% of 46.6 (8) min after 150 µg kg^{-1} or 68.3 (2.4) min after 200 µg kg^{-1}).[8 12] Furthermore, in our study the total dose was given in increments and therefore recovery from the first dose could have started while the last dose was being administered. This could result in underestimation of duration of action, particularly during the TIVA technique.

Mean recovery index$_{25-75\%}$ was 11.9 min in the TIVA group, in accordance with data obtained during previous investigations with barbiturate–opioid–nitrous oxide anaesthesia after a dose of 100 µg kg^{-1} (8 min[12] and 12.6 min[8]).

In summary, interaction of cisatracurium and potent inhalation anaesthetics results in potentiation of depression of T1/T0 and a leftward shift in the dose–response relationship. We used repetitive incremental dosing until 95% depression of the first twitch (end-point) was obtained in an individual patient (equi-effective dose). Using this approach of equi-effective dosing, potentiation was demonstrated in terms of ED_{50} and ED_{95} for all inhalation anaesthetics, whereas prolongation of duration of neuromuscular block was less pronounced. In contrast, if neuromuscular blocking drugs are given in identical fixed doses, regardless of the individual effective dose, differences in duration of action become more evident.

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Effects of hypothermia on thrombelastography in patients undergoing cardiopulmonary bypass

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Summary

Thrombelastography (TEG) correlates with postoperative chest drain output in patients undergoing cardiopulmonary bypass (CPB). *In vitro* incubation with heparinase allows TEG monitoring during CPB, despite heparin anticoagulation. Hypothermia impairs coagulation, but these effects cannot be assessed by standard coagulation tests performed at 37 °C. The aim of this study was to assess the effects of hypothermia on TEG. Therefore, we have compared normothermic and temperature-adapted TEG in 30 patients undergoing CPB. Our data showed significantly impaired reaction time (*r*), kinetic time (*k*), and angle α (α) in temperature-adapted compared with normothermic TEG. Maximum amplitude (MA), reflecting absolute clot strength, was not affected at temperatures of 33–37 °C. These findings indicate a decrease in the speed of clot formation, but not absolute deterioration in clot quality. Furthermore, heparinase-modified TEG indicated that there were nine cases in which heparin effects persisted after heparin reversal with protamine, providing a rational guide to protamine therapy. (*Br. J. Anaesth.* 1998; **80**: 313–317)

Keywords: measurement techniques, thrombelastography; heart, cardiopulmonary bypass; surgery, cardiovascular; hypothermia; blood, anticoagulants, heparin

Severe bleeding is a major complication of cardiopulmonary bypass (CPB) for open heart surgery. Various causes are known and have been investigated, for example platelet dysfunction, haemodilution, contact activation by the artificial surface of the CPB, heparin excess and inadequate heparin reversal.[1] Hypothermia induced during CPB to reduce neuronal damage may also impair coagulation. Patients undergoing hypothermic CPB show a tendency towards increased intraoperative and postoperative blood loss and an increased rate of re-operation for bleeding.[2-4]

However, the influence of hypothermia on the haemostatic system cannot be assessed by standard coagulation tests, as these tests are performed at 37 °C. Thrombelastography (TEG) is an easy and reliable coagulation monitoring system which can be performed at different temperatures.[5] In patients undergoing CPB, TEG performed at 37 °C correlates with postoperative chest tube drainage and predicts postoperative bleeding better than activated clotting time (ACT), routine coagulation screen tests or Sonoclot measurements.[6 7]

To prevent clotting in the extracorporeal oxygenator, unfractionated heparin is given before CPB, making it impossible to perform TEG with native whole blood. *In vitro* incubation with heparin-utilizing substances allows TEG monitoring during bypass, despite anticoagulation with heparin.[8]

Protamine is used for antagonism of heparin. In the absence of heparin, protamine *per se* may affect coagulation tests.[9] Thus the heparin-to-protamine ratio has to be adequate to avoid either heparin or protamine excess leading to prolongation of coagulation tests. Heparinase, an enzyme isolated from *Flavobacterium heparinum*, uses heparin without affecting coagulation tests in the absence of heparin.[10] For TEG, heparinase neutralizes high doses of heparin, enabling TEG monitoring during CPB.[8] The use of heparinase-modified, temperature-adapted TEG permits assessment of the effects of hypothermia on TEG during CPB.

Only one study has investigated the influence of hypothermia on TEG monitoring in patients undergoing liver transplantation.[11] The aetiology of coagulopathy is different during liver transplantation and open heart surgery with the use of CPB. During CPB, coagulation is affected by haemodilution and contact activation, and blood is anticoagulated to prevent clotting in the extracorporeal oxygenator. The aetiologies of hypothermia are also different. Whereas it is therapeutically indicated during CPB, hypothermia occurs accidentally during liver transplantation and can be avoided by surface warming.[12]

We have assessed the effects of hypothermia on TEG monitoring in patients undergoing CPB. We compared TEG performed at 37 °C and at body core temperature before, during and after CPB. To allow TEG during anticoagulation with heparin, we performed native and heparinase-modified measurements. Moreover, comparison of native and heparinase-modified TEG after protamine adminis-

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tration may indicate the incidence of inadequate heparin reversal after CPB.

Patients and methods

After obtaining local Ethics Committee approval and informed consent, we studied 30 consecutive patients. Inclusion criteria were age >18 yr and elective primary coronary revasculation with the use of CPB under mild hypothermia. Exclusion criteria were the use of platelet altering medications within 1 week of surgery, pre-existing bleeding disorders or diabetes with severe peripheral vascular complications.

The extracorporeal circuit consisted of a membrane oxygenator with polyvinyl chloride tubing, non-occlusive roller pumps and a cardiotomy reservoir (William Harvey, USA). The oxygenator was primed with crystalloid solution 2000 ml and 20% mannitol 100 ml, containing unfractionated heparin 8000 u. and aprotinin 1 × 10^6 ku. (Trasylol, Bayer, Austria). CPB was performed with a flow rate of 2.5 litre min^{-1} m^{-2} and moderate hypothermia. Blood was cooled to 32 °C during the hypothermic phase of CPB and warmed to 37 °C during rewarming; the rate of cooling and warming was controlled to approximately 1 °C min^{-1}. We monitored blood temperature using a pulmonary artery flotation catheter, oesophageal temperature and bladder temperature. As oesophageal temperature may be influenced by cold cardioplegia solution[13] and as we wished to avoid overestimation of hypothermia, we considered bladder temperature as body core temperature. We did not use the temperature recorded with the pulmonary artery flotation catheter because of reduced lung perfusion during CPB.

Patients were given unfractionated heparin 300 u. kg^{-1} (Heparin Immuno, Immuno, Austria) before aortic cannulation to achieve an activated clotting time (ACT) of >450 s (Hemochron 800, Intern. Technidine Corp., USA). If ACT was < 450 s after administration of this initial dose, an additional bolus dose of heparin 100 u. kg^{-1} was given. ACT was monitored every 30 min until the end of CPB. If ACT was less than 400 s during CPB, additional boluses of heparin 100 u. kg^{-1} were given. The initial heparin dose necessary to achieve an ACT >450 s was neutralized after the end of CPB by protamine (Protamin Roche, Hoffmann-La Roche, Switzerland) in a ratio of 1:1.

Blood samples were obtained from an arterial cannula (or from the port of the oxygenator during CPB) before skin incision; after heparin administration; 10 min after the start of CPB; at the lowest body core temperature during CPB; immediately before protamine administration; and at the end of surgery. Samples were collected in silicone-coated glass tubes containing buffered sodium citrate 0.129 mol $litre^{-1}$ (Vacutainer, Becton Dickinson, France).

We performed four TEG measurements simultaneously on each blood sample at 37 °C and at core temperature, using native and heparinase-modified blood. Temperature-adapted measurements were not performed when body temperature was 36.5 °C or higher. TEG was performed with 300 μl of citrated whole blood and 60 μl of 0.645% $CaCl_2$. For heparinase-modified measurements, blood was incubated in heparinase vials (Hemoscope, USA) containing heparinase 4 u./ml of blood. Four commercially available temperature-adaptable Thrombelastographs D (Hemoscope, USA) were used for this investigation.

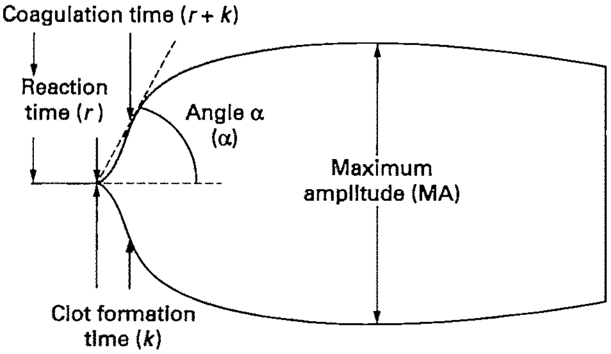

Figure 1 Normal thrombelastogram trace. Normal ranges: r = 10–19 mm, k = 4–10 mm, α = 44–55° and MA = 50–64 mm.

TEG reaction time (*r*) is the time from the start of measurement until initial fibrin formation. Clot formation time (*k*) measures the time necessary to reach 20 mm of clot strength. Coagulation time (*r+k*) is the sum of *r* and *k* (fig. 1). Values for *r*, *k* and *r+k* are expressed in millimetres (mm), as the chart speed is 2 mm min^{-1} and the time in minutes is equal to the distance in mm divided by 2 (normal ranges: *r* 10–19 mm; *k* 4–10 mm). The angle α measures the rapidity of fibrin build-up and cross-linking, which is the speed of clot strengthening (normal range 44–56°). Maximum amplitude (MA) measures maximum clot strength which is dependent on platelet function and, to a lesser extent, on fibrinogen level (normal range 50–64 mm) (fig. 1).[5]

The accuracy of temperature measurement in the TEG was verified by measuring the temperature of the thrombelastograph cuvettes filled with normal saline before the investigation. The accuracy of temperature measurement between 28 °C and 37 °C was within ± 0.2 °C. Measurements were performed with prewarmed (28 °C) disposable plastic pins and cups (Haemoscope, USA) which were inserted at least 10 min before measurement to confirm the exact temperature.

STATISTICAL ANALYSIS

After testing for normal distribution of the data, we performed ANOVA for repeated measurements to test the effects on TEG variables. The Newman–Keuls test was used to test for differences between normothermic and temperature-adapted TEG. To compare native and heparinase-modified measurements at the end of surgery, a *t* test for dependent samples was used. Statistical significance was considered at $P < 0.05$. All values are expressed as mean (SD).

Results

Thirty patients (24 males, six females; mean age 68.1 (range 40–85) yr; mean height 171.5 (SD 10.8) cm; mean weight 75.4 (12.8) kg) underwent surgery for 3.5 (0.7) aortocoronary bypass procedures. Extracorporeal circulation time was 94.6 (17.6) min, with an aortic clamping time of 52.7 (12.5) min. To achieve adequate anticoagulation, heparin 29 056 (11 880) u. were given. To reverse heparin after CPB,

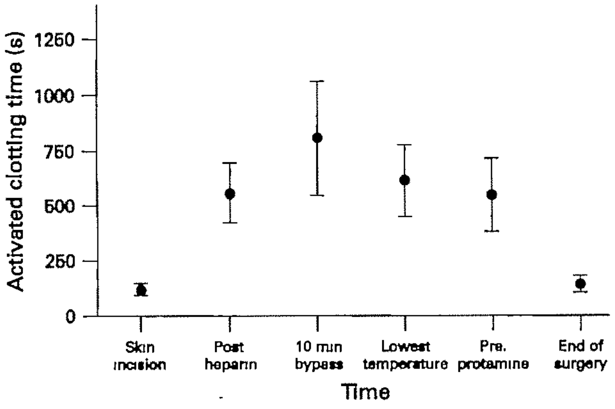

Figure 2 Activated clotting time in 30 patients undergoing cardiopulmonary bypass at the times indicated (mean (SD)).

Table 1 Body core temperature in 30 patients undergoing cardiopulmonary bypass at the times indicated

	Temperature (°C)		
	Mean (SD)	Maximum	Minimum
Skin incision	36.2 (0.2)	37.1	35.5
After heparin	35.7 (0.5)	37.1	34.8
10 min bypass	34.3 (1.3)	36.2	30.6
Lowest temperature	33.3 (1.6)	35.8	29.8
Before protamine	36.2 (0.3)	37.5	35.7
End of surgery	36.2 (0.2)	37.3	35.6

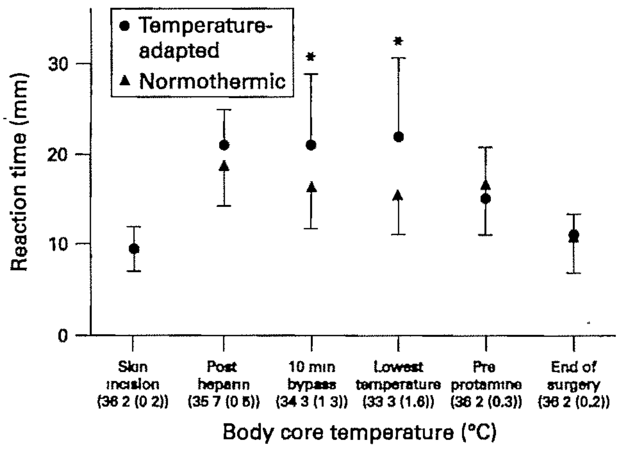

Figure 3 Temperature-adapted and normothermic reaction time (r) in 30 patients undergoing cardiopulmonary bypass (mean (SD)). $*P < 0.05$ temperature-adapted *vs* normothermic values.

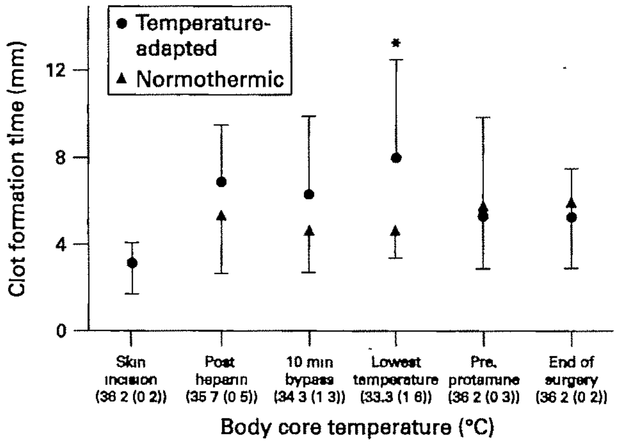

Figure 4 Temperature-adapted and normothermic clot formation time (k) in 30 patients undergoing cardiopulmonary bypass (mean (SD)). $*P < 0.05$ temperature-adapted *vs* normothermic values.

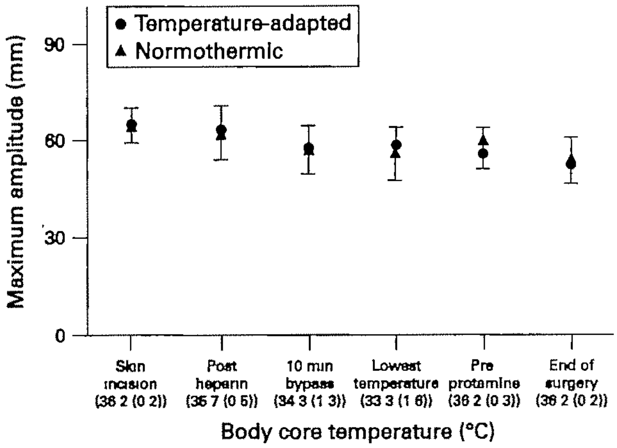

Figure 5 Temperature-adapted and normothermic maximum amplitude (MA) in 30 patients undergoing cardiopulmonary bypass (mean (SD)).

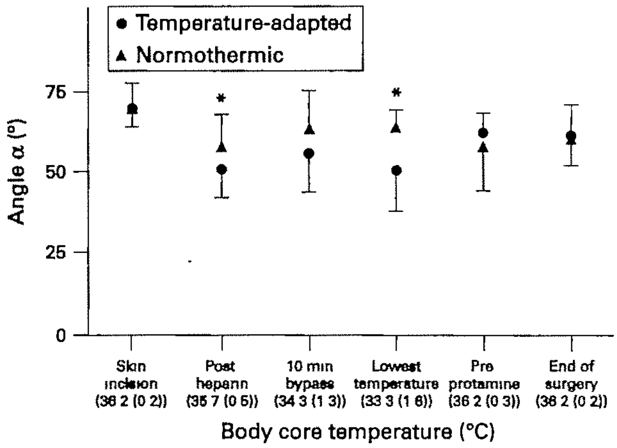

Figure 6 Temperature-adapted and normothermic angle α in 30 patients undergoing cardiopulmonary bypass (mean (SD)). $*P < 0.05$ temperature-adapted *vs* normothermic values.

protamine 26 997 (8966) u. were given (fig. 2). The course of body core temperature is shown in table 1.

Data on temperature-adapted and normothermic TEG variables, resulting from heparinase-modified measurements, are shown in figures 3–6. Body temperature reduction to 33.3 (1.6) °C during CPB prolonged r by approximately 50% and k by approximately 70% in the temperature-adapted measurements compared with the normothermic measurements. The angle α decreased by approximately 30%. MA was not affected by temperatures of 33–37 °C, but decreased significantly during surgery in normothermic and temperature-adapted measurements.

At the time of skin incision, before administration of heparin, native and heparinase-modified measurements did not differ. After administration of heparin, native TEG measurements resulted in straight lines after 60 min in all cases. At the end of surgery, after heparin reversal with protamine, native and heparinase-modified TEG were different (table 2). In nine cases heparinase-modified measurements were improved compared with native measurements (table 2). Coagulation time was the best indicator for remaining heparin effects (fig. 7).

Discussion

We have demonstrated that the heparinase-modified TEG showed significantly impaired r, k and α values in temperature-adapted measurements compared

Table 2 Native and heparinase-modified TEG variables at the end of surgery after heparin reversal with protamine. *$P<0.05$ native *vs* heparinase-modified measurements for all cases; †$P<0.05$ native *vs* heparinase-modified measurements for cases with remaining heparin effects ;‡$P=0.05$ native *vs* heparinase-modified *k* measurements for cases with remaining heparin effects (mean (SD))

	Native TEG (all cases)	Heparinase-modified TEG (all cases)	Native TEG of cases with heparin effects	Heparinase-modified TEG of cases with heparin effects
r (mm)	11.8 (3.9)	10.7 (3.7)*	11.6 (3.4)	9.0 (2.1)†
k (mm)	6.8 (4.1)	5.8 (2.9)	8.3 (5.6)	5.1 (1.8)‡
MA (mm)	51.1 (7.2)	52.8 (7.9)	49.9 (9.0)	54.5 (6.7)†
α (°)	54.8 (11.8)	59.6 (11.5)*	49.6 (13.9)	62.4 (10.2)†

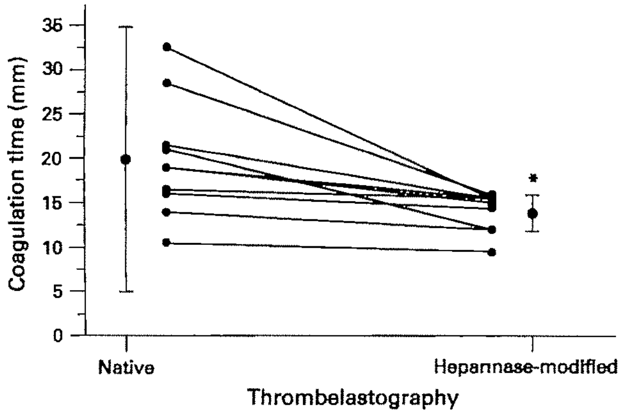

Figure 7 Native and heparinase-modified coagulation time in nine patients with remaining heparin effects after administration of protamine at the end of surgery (mean (SD)). *$P < 0.05$ heparinase-modified *vs* native values.

with normothermic measurements during CPB. Similar results have been shown in hypothermic patients during liver transplantation.[11] Reaction time (*r*) represents the time necessary for building the first fibrin strands, *k* the time for reaching a certain clot strength and α represents the formation rate of the clot. Reaction time is dependent mainly on coagulation factor activity, whereas *k* and α depend on plasma coagulation and the interaction of platelets with fibrin, increasing clot stability. Impairment of these variables by temperature reduction indicates a reduction in activity of both coagulation factors and platelet function. In patients undergoing CPB, *r*, *k* and α are affected by a temperature reduction of 3.7 °C leading to an approximate 50% reduction in coagulation, as assessed by TEG. Performing ***heparinase-modified*** TEG at 37 °C in hypothermic patients may lead to underestimation of coagulopathy during CPB when hypothermia is not considered.

However, temperature-adapted TEG could lead to inappropriate therapeutic interventions if prolongation in TEG is caused by hypothermia and treated with administration of coagulation factor. Therefore, it seems appropriate to treat patients with coagulation factors or platelets only when results of normothermic TEG are abnormal. In the treatment of hypothermic patients with bleeding disorders, comparison of temperature-adapted and normothermic TEG can help to guide therapeutic interventions, for example administration of coagulation factor, transfusion of platelets, active warming or surgical re-exploration. As hypothermia impairs coagulation, it should be treated. The literature shows a decrease in blood loss in patients undergoing normothermic CPB compared with those undergoing hypothermic CPB, without an increase in adverse systemic effects.[2,4]

Maximum amplitude (MA) reflects absolute clot strength and not coagulation time, unlike *r* and *k*. Temperatures between 33 °C and 37 °C do not affect MA. This finding, together with prolonged *r*, *k* and a smaller α value, indicates a decrease in the speed of clot formation, but not absolute deterioration in clot quality, which is represented by MA. In the course of surgery MA decreased for normothermic and temperature-adapted measurements in the same manner. This indicates that TEG is able to detect impairment of platelet function caused by surgery and the extracorporeal circulation.

Two investigations showed prolongation in plasma coagulation tests caused by *in vitro* reduction of the assay temperature.[14,15] Thrombin time (TT) was less prolonged than prothrombin time (PT) and activated partial thromboplastin time (APTT). It was concluded that there may be a cumulative effect in multi-step assays, such as PT or APTT, leading to greater prolongation than in one-step assays, such as TT. Prolongation of approximately 50–60% in PT and APTT was found at 29 °C or 28 °C, respectively.[14,15] Our data showed 50–60% prolongation of TEG variables at 33.3 °C. TEG is a global assessment of haemostatic function, documenting the interaction of platelets with the protein coagulation cascade from the time of initial fibrin formation through platelet aggregation, clot strengthening and fibrin cross linkage to eventual clot lysis.[5] It is a multi-step assay of many more stages than plasma coagulation tests such as PT or APTT. The high sensitivity of TEG to temperature may be caused by cumulative slowing of the enzymatic steps of coagulation, as assessed by TEG. Alternatively, either interaction of platelets with coagulation proteins or platelet function *per se*, might be especially sensitive to the effects of hypothermia. Hypothermia-induced reversible platelet dysfunction was shown in an animal study by Valeri and colleagues.[16] In patients undergoing CPB, hypothermia reduced intraoperative platelet function and platelet recovery in the post-bypass period.[3] In that study, aprotinin reduced the negative effects of hypothermic CPB on platelet function. Although our patients received aprotinin in a much lower dose, impairment of TEG variables by temperature may be even higher when no aprotinin is given. Furthermore, aprotinin reduces clot lysis, as assessed by TEG. In fact, we found no differences in TEG clot lysis in normothermic compared with temperature-adapted measurements in our study. Only further study of the enzymatic activity of coagulation proteins and platelet activity under conditions of hypothermia will determine the extent to which different mechanisms contribute to hypothermia-induced coagulopathy.

Data in figures 3–6 are from heparinase-modified measurements. The heparinase-modified measurements, whether temperature-adapted or not, were not different compared with the corresponding native measurements before heparin administration. This shows that heparinase *per se* does not affect TEG and correlates with the findings of other investigations.[8 17]

The heparinase-modified TEG provides useful additional information compared with native TEG. At the end of surgery, after heparin reversal with protamine, nine cases of heparinase-modified TEG were improved compared with native TEG (fig. 7, table 2). These TEG measurements showed remaining heparin effects, which can increase bleeding after CPB. Comparison of native with heparinase-modified TEG is a useful guide when reconsidering protamine therapy after CPB.

In summary, our data showed reductions in coagulation caused by hypothermia, indicating the high sensitivity of TEG to temperature. Heparinase-modified TEG detected heparin effects remaining after heparin reversal with protamine. This could provide a rational guide to protamine therapy after CPB.

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British Journal of Anaesthesia 1998; **80**: 318–323

Benefits of intraoperative skin surface warming in cardiac surgical patients

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Summary

We have investigated patients undergoing cardiac surgery with hypothermic bypass to see if the addition of skin surface warming during systemic rewarming on bypass (heated group, n = 43) would improve perioperative thermal balance compared with conventional management without skin warming (control group, n = 43) in an open, randomized, controlled study. Intraoperative skin warming with a water mattress and forced warm air over the face, neck and shoulders attenuated the afterdrop in nasopharyngeal temperature after weaning from bypass (2.3 (1.2) °C and 1.3 (0.5) °C in the control and heated groups, respectively) (P < 0.05) and resulted in higher rectal temperature 4 h after surgery. Despite similar standard coagulation tests, heated patients had lower blood loss via the chest tubes (600 (264) ml *vs* 956 (448) ml in control patients) (P< 0.05) and less requirements for i.v. colloid infusion (1662 (404) ml *vs* 1994 (389) ml) (P < 0.05). There was a significant inverse correlation between rectal temperature on arrival in the ICU and postoperative blood loss (r = 0.57, P < 0.001). These data suggest that additional skin surface warming with a water mattress and forced warm air helped to preserve perioperative thermal balance and may contribute to reduced bleeding after cardiac surgery. (*Br. J. Anaesth.* 1998; **80**: 318–323)

Keywords: temperature, body; equipment, warming devices; surgery, cardiovascular; blood, coagulation; hypothermia

Hypothermia remains a common problem because of its deleterious haemodynamic, haemostatic, immune and metabolic effects.[1–4] After non-cardiac surgery, mild hypothermia has also been associated with arterial hypertension and myocardial ischaemia,[5] in addition to increased blood loss.[6]

Patients undergoing cardiac surgery are often cooled to nasopharyngeal temperatures of 26–28 °C. At the end of cardiopulmonary bypass (CPB), even though nasopharyngeal temperature is restored to pre-bypass levels, a considerable mass of peripheral tissues remains at subnormal temperatures; subsequent redistribution of heat from the core to the periphery causes a decrease in nasopharyngeal temperature ranging from 1 to 3 °C, termed "afterdrop".[7 8] During operation, adopting a "normothermic" bypass technique, prolonging the rewarming period or infusing vasodilators while increasing pump flow may attenuate the postoperative central temperature afterdrop.[9] In the intensive care unit (ICU), external heat, that is convective or radiant, applied over a large body surface area has been shown to accelerate rewarming with the benefits of less shivering, lower oxygen demand and more haemodynamic stability.[10–13]

Although skin surface warming with a forced warm air device is a simple, safe and efficient means for preventing hypothermia during major surgical procedures,[14] it has not yet been recommended for use during cardiac surgery because the body surface area available for cutaneous warming was thought to be too small.

As the afterdrop in nasopharyngeal temperature is attributed to redistribution of heat from the warm core to the cold peripheral compartment, we hypothesized that the addition of skin warming to heat exchange via the bypass membrane would improve body rewarming and help to preserve body heat content, thereby minimizing the afterdrop in core temperature. Therefore, we investigated if concomitant intraoperative use of a heating water mattress and forced warm air over a limited body surface area (head and neck) would effectively prevent hypothermia and attenuate chest blood loss in the early period after cardiac surgery.

Patients and methods

After obtaining hospital Ethics Committee approval and written informed consent, we studied 91 patients undergoing elective coronary artery bypass graft surgery, aortic valve replacement and mitral valve repair or replacement. Patients with severe left ventricular dysfunction based on clinical history (dyspnoea grade 3 or higher) and ventricular angiograms (left ventricular ejection fraction <30%) were excluded. In addition, in the early postoperative period, those patients with active bleeding requiring surgical haemostasis were retrospectively excluded. Usual cardiac medications, including nitrates, β-blockers and calcium channel blockers were administered up to the morning of surgery. After an overnight fast, patients were premedicated with morphine 7.5 mg i.m. and diazepam 5–10 mg orally, 1 h before opera-

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tion. In the induction room, peripheral venous, radial arterial and central venous catheters were inserted for fluid and drug administration and for haemodynamic monitoring. A transoesophageal echocardiographic probe was inserted after tracheal intubation. General anaesthesia was conducted according to standard practice by an experienced anaesthetist not involved in the study and was based on moderate doses of fentanyl (40–60 μg kg^{-1}) and midazolam (0.03–0.06 mg kg^{-1} followed by 0.10 mg kg^{-1} h^{-1}) with pancuronium for neuromuscular block (0.15 mg kg^{-1} at induction and 0.05 mg kg^{-1} during bypass). Mechanical ventilation was adjusted to maintain normocapnia and normoxia. Body temperature was recorded continuously with calibrated thermistors (AS3 Datex Instrum. Corp. Helsinki, Finland) placed in the nasopharynx and in the rectum; nasopharyngeal and rectal temperatures indicated the temperature of the body core and muscular compartments.[8] All probes were accurate to ± 0.1 °C over the range 20–40 °C.

After aortic and right atrium cannulation, nonpulsatile CPB was commenced with a membrane oxygenator primed with crystalloids 2 litre and body temperature was decreased to achieve moderate hypothermia (lowest nasopharyngeal temperature 28.6 (2.4) °C and 28.9 (2.9) °C in the control and heated groups, respectively). After aortic clamping, myocardial protection was provided with St Thomas's solution 600–900 ml infused via the aortic root at 25–30-min intervals. During CPB, pump flow greater than 2 litre min^{-1} m^{-2} was maintained during moderate hypothermia and increased to 2.4 litre min^{-1} m^{-2} during rewarming. Vasodilators (nitroprusside) or vasoconstrictors (phenylephrine) were administered to maintain mean arterial pressure (MAP) within an acceptable range (60–80 mm Hg). After completion of surgical revascularization or valve repair–replacement, and when rectal temperature was greater than 35.7 °C, patients were weaned from CPB. Administration of nitroglycerin 1–3 mg h^{-1} i.v. was part of our standard management procedure, which was started during rewarming and continued until 6–8 h after surgery.

In the ICU, patients underwent mechanical ventilation throughout the 12-h study and, according to routine medical care, repeated bolus doses of morphine 1 mg were given during emergence from anaesthesia and when increases in heart rate and arterial pressure were interpreted as pain, anxiety or discomfort.

During and after operation, a heat and moisture filter (Pall breathing system, Newquay, UK) was connected to the Y-piece of the non-rebreathing respiratory system. Ambient temperature was maintained at 18–20 °C in the operating theatre and at 22–24 °C in the ICU.

MEASUREMENTS AND CALCULATIONS

During operation, nasopharyngeal and rectal temperatures were recorded at the following times: 10–15 min before aortic cannulation; at the end of each cardioplegia; after aortic unclamping; after separation from CPB; and during sternal and skin closures. Total duration of rewarming on bypass was recorded and the afterdrop was calculated as the difference between nasopharyngeal temperature at the time of separation from CPB and the lowest nasopharyngeal temperature recorded before transfer to the ICU.

After operation, activated clotting time and platelet count were measured on arrival in the ICU; systemic haemodynamic variables (MAP, heart rate, cardiac output) and rectal temperature were recorded hourly for 8 h and at 10 and 12 h after the end of surgery.

Urinary volume, blood loss through the chest tubes, i.v. fluid requirements (crystalloids and colloids), transfusion of blood products and the need for additional vasodilators (nitroprusside) and inotropic support (dobutamine or dopamine >5 μg kg^{-1} min^{-1}, norepinephrine or epinephrine >0.05 μg kg^{-1} min^{-1}) were also recorded.

EXPERIMENTAL DESIGN

On the day of surgery, patients were allocated randomly to routine thermal management (control group) or to additional skin warming (heated group). In both groups, core body rewarming (systemic rewarming) was accomplished by heat exchange through the oxygenator (maximum gradient of 10 °C between the patient's blood temperature and water temperature in the oxygenator). In the heated group, extra warming of the skin included transfer of convective heat with a Bair Hugger system (Bair-Hugger Model 500, Augustine SA, Berne, Switzerland) and conductive heat with a thermostatic water mattress (Thermostat T1000, JMW Medical Systems Ltd, Midlothian, UK). Heated patients lay on a mattress containing circulating water at 38 °C (5 litre with a mean flow of 3–4 litre min^{-1}) in contact with approximately 0.3–0.4 m^2 of body surface area (from the buttocks up to the shoulders) while forced warm air (at 38 °C) created a high velocity "wind" over the head, neck and shoulders (10–15% of body surface area) under a simple blanket. Systemic and skin rewarming were started during completion of the last distal graft anastomosis or at the end of valvular repair. Systemic rewarming ended when rectal temperature had reached 35.7 °C in the two groups, while skin rewarming was continued until skin closure (in the heated group).

In the ICU, nurses and physicians administering fluids and treating pain were blinded to the patient's group.

STATISTICAL ANALYSIS

Parametric data were expressed as mean (SD) and analysed using two-way analysis of variance with Dunnett's test for within-group changes with respect to baseline. The relationships between chest tube fluid losses (dependent variable) and other independent variables, such as rectal temperature, afterdrop, length of CPB and aortic clamping were studied by uni- and multiple stepwise regression analysis. Pearson product-moment or Spearman rank correlation coefficients were calculated depending on the parametric or non-parametric nature of the data. Drug treatment, need for transfusion and type of surgery were compared using chi-square with Yates' correction. Differences were considered significant at $P < 0.05$.

Results

We studied 91 patients; two patients in each group were subsequently excluded because of bleeding which required surgical haemostasis within the first 3 h after operation. Another patient in the control group died within 2 h after surgery in cardiac failure as a result of a massive myocardial infarct.

Preoperative clinical, surgical and anaesthetic data are summarized in table 1. The two groups were similar in patient characteristics and surgical data. The risk of bleeding, as indicated by the type of surgery (combined valvular surgery and myocardial revascularization) and the use of aprotinin or antiaggregant and anticoagulant medications were also comparable in the two groups. Activated clotting time and platelet count were similar on arrival in the ICU, in addition to packed cell volume at the end of the study. Postoperative shivering requiring administration of pethidine or a muscle relaxant was observed in five patients in the heated group and in nine patients in the control group.

PERIOPERATIVE BODY TEMPERATURE

Duration of systemic rewarming and the gradients between nasopharyngeal and rectal temperatures after weaning from CPB did not differ between the two groups (table 2). However, body temperature was better maintained in the heated group, as: (1) the afterdrop in nasopharyngeal temperature was smaller; (2) fewer patients presented with nasopharyngeal temperatures less than 35.5 °C at the end of surgery (15 and 28 patients in the heated and control groups, respectively) ($P < 0.05$); and (3) rectal temperature was significantly higher from the time of sternal closure up to 4 h after operation (fig. 1).

In the control patients, rectal temperature on arrival in the ICU was 35.3 (0.4) °C and increased at a rate of approximately 0.3 °C h^{-1}, whereas in the heated group, initial postoperative rectal temperature was 36.0 (0.4) °C and increased more slowly (approximately 0.2 °C h^{-1}) over the subsequent 6 h. At the end of the 12-h study, rectal temperatures did not differ between the two groups (37.5 (0.5) °C in the heated and 37.4 (0.5) °C in the control group).

There was no significant association between the afterdrop in nasopharyngeal temperature and aortic clamping time ($r = 0.12$), CPB duration ($r = 0.09$), lowest temperature during CPB ($r = 0.08$) or body surface area ($r = 0.25$) in the two groups. In the control group only, the afterdrop in nasopharyngeal temperature was significantly correlated with the ratio of rewarming time to duration of aortic clamping ($r = 0.86$); in these patients, duration of systemic rewarming, representing >80% or <80% of clamping time, was associated with an afterdrop in nasopharyngeal temperature of −1.7 °C or −2.5 °C, respectively.

HAEMODYNAMIC STATE

Haemodynamic data (heart rate, MAP and cardiac output) were comparable in the two groups in addition to requirements for inotropic or, vasopressor support (15 patients in the heated group and 20 patients in the control group) and for additional vasodilators (five patients in the heated group and seven in the control group). Nitroglycerin was administered at a median rate of 2 mg h^{-1} in the two groups and over a median period of 8 h in the control group and 7 h in the heated group.

Table 1 Clinical, surgical and anaesthetic data (mean (range) or number of patients). No significant differences between groups

	Heated group (n=43)	Control group (n=43)
Patient characteristics		
Age (yr)	60 (42–76)	66 (50–85)
Sex (M/F)	34/9	35/8
Body surface (m^2)	1.9 (1.6–2.1)	1.9 (1.6–2.2)
Left ventricular ejection fraction (%)	61 (31–88)	63 (33–84)
Preoperative antiaggregant and anticoagulant treatment		
Salicylates (n)	23	18
Heparin (n)	5	1
Dicoumarol (n)	1	1
Surgical procedures		
CABG (n)	30	29
Valvular surgery (n)	9	8
Combined (n)	4	6
Aortic clamping (min)	99 (18–181)	101 (29–250)
CPB duration (min)	138 (49–217)	142 (48–297)
Anaesthesia, analgesia and sedation		
Fentanyl (μg kg^{-1})	58 (39–92)	61 (31–96)
Midazolam (mg kg^{-1})	0.7 (0.4–1.1)	0.8 (0.5–1.2)
Morphine (mg kg^{-1})	0.12 (0.04–0.19)	0.10 (0.03–0.17)

Table 2 Rewarming time, gradients of nasopharyngeal to rectal temperature and afterdrop in nasopharyngeal temperature (mean (SD) or number). *P<0.05 between groups

	Heated group (n=43)	Control group (n=43)
Rewarming on bypass (min)	71 (21)	77 (22)
Afterdrop in nasopharyngeal temp. (°C)	−1.3 (0.5)	−2.3 (1.2)*
Gradients of nasopharyngeal to rectal temp. (°C)		
Aortic unclamping	2.1 (1.9)	2.5 (2.0)
Weaning from bypass	0.7 (0.9)	0 6 (0.8)
Sternal closure	−0.6 (0.4)	−0.5 (0.8)
End of surgery	−0.6 (0.5)	−0.7 (0.4)

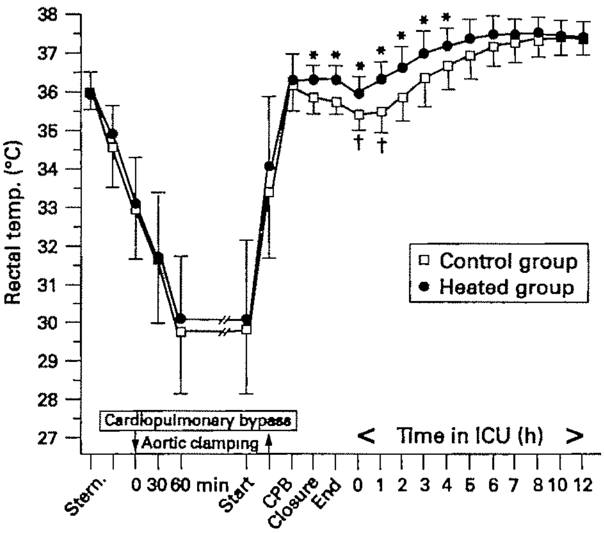

Figure 1 Perioperative changes in rectal temperature in patients undergoing cardiac surgery with standard intraoperative thermal management (control group) and in those with additional skin warming (heated group). Significant differences ($P < 0.05$): *between the two groups; †compared with values at weaning from CPB in the same group.

Table 3 Intra- and postoperative fluid balance and blood coagulation tests on arrival in the ICU (mean (range) or number). *$P<0.05$ compared with control group

	Heated group (n=43)	Control group (n=43)
Intraoperative fluid balance		
I.v. crystalloids (ml)	2149 (700–4500)	2158 (1000–4100)
I.v. synthetic colloids (ml)	345 (0–1900)	414 (0–2100)
Cardioplegic solution (ml)	1929 (300–5900)	1673 (300–4500)
Autologous blood (ml)	548 (190–1500)	566 (100–2050)
Red blood cell (n)	17	18
Fresh frozen plasma (n)	8	5
Urine ouput (ml)	1843 (300–5550)	1940 (450–4000)
Postoperative fluid balance		
Crystalloids (ml)	1891 (600–4350)	2227 (750–4950)
Colloids (ml)	1662 (500–3500)*	1994 (1000–4450)
Red blood cells (n)	6	13
Fresh frozen plasma (n)	7	13
Chest tube (ml/12 h)	660 (230–1870)*	956 (340–5480)
Urine output (ml/12 h)	1877 (195–3450)	1862 (250–3850)
Blood coagulation tests in ICU		
Activated coagulation time (s)	121 (84–175)	118 (78–164)
Platelets (number/ml)	109 (81–161)	116 (82–158)

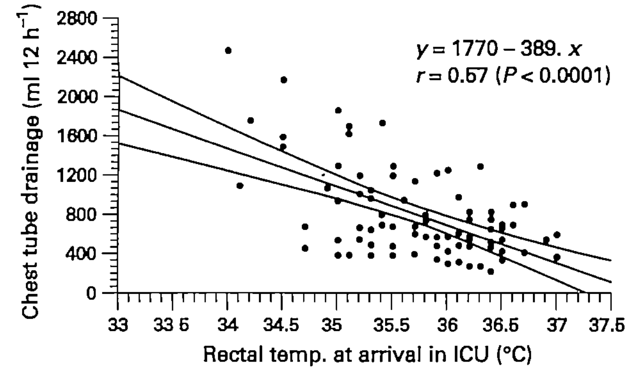

Figure 2 Relationship between fluid loss via the chest tubes over the first 12 h after cardiac surgery and rectal temperature on arrival in the ICU (regression line and 95% confidence intervals).

FLUID BALANCE AND HAEMOSTATIC VARIABLES

During operation, i.v. clear fluids, transfusion of homologous blood products and urine output did not differ between groups. During the first 12 h in the ICU, the amount of blood loss through the chest tubes was smaller in the heated group (−31%, $P < 0.05$) and was accompanied by reduced i.v. infusion of fluids (−23%, $P < 0.05$) compared with the control group (table 3). Transfusion of homologous blood components tended to be reduced in the heated group, although this was not significant (seven patients compared with 13 patients in the control group). There was a significant inverse relationship between rectal temperature on arrival in the ICU and postoperative fluid loss via the chest tubes in the pooled data for the two groups ($r = -0.57$, $P < 0.0001$). Regression analysis between these two variables is illustrated in figure 2.

Discussion

As expected, many patients became hypothermic at the end of cardiac surgery, despite systemic rewarming until rectal temperature reached at least 35.7 °C, and when no precautions were taken to avoid "redistribution hypothermia". In contrast, intraoperative combination of two simple skin warming methods (Bair Hugger and water mattress) in addition to core rewarming attenuated the core temperature afterdrop and resulted in higher rectal temperatures in the early hours after CPB. Importantly, better thermal homeostasis was associated with reduced postoperative fluid losses and i.v. fluid requirements.

Application of skin warming did not adversely affect the working conditions in the operating theatre compared with the routine management procedure. Additional noise was barely noticeable, i.v. cannulae were secured on the operating table, the patient's face and eyes were · checked regularly and the transoesophageal echocardiographic probe was manipulated easily.

THERMAL BALANCE

In unwarmed patients, a core temperature afterdrop of −2 °C has been associated with a heat deficit of more than 300 kJ which is equivalent to basal heat production over 1–2 h and requires 50–100% increase in energy expenditure in the early postoperative period.[7 15] In this study, we hypothesized that heat storage in peripheral tissues would reduce the core-to-periphery gradient and attenuate heat flow redistribution. In the heated group, skin warming with forced warm air and a water mattress resulted in a mean decrease in nasopharyngeal temperature of 39% less and a higher rectal temperature during the first 4 h in the ICU compared with control patients. Presumably, higher mean body temperature (+0.8 °C compared with the control group) was associated with better restoration of body heat content after weaning from bypass (approximately +195 kJ in a 70-kg adult) and with diminished thermoregulatory responses to cold, as indicated by a slower postoperative increase in rectal temperature in heated patients (0.2 °C h^{-1} compared with 0.3 °C h^{-1} in control patients).

During non-cardiac surgery, when 80–90% of the body surface is exposed to forced warm air (38 °C), a large amount of heat (approximately 200 kJ h^{-1}) has been shown to be transferred across the skin.[16] During cardiac surgery, despite a smaller surface available (only 10–15% of the total body surface), transfer of convective heat was likely facilitated by several factors, namely the underlying highly perfused anatomic structures of the upper body, large air–skin temperature difference, prolonged duration of rewarming (2–2.5 h) and a high velocity convective "wind". Interestingly, heat transfer has been shown to be twice as effective when forced air is delivered beneath a simple bed sheet instead of using a commercial blanket whose rigid nature prevents the close approximation to non-planar anatomical structures and whose pinhole gridwork pattern causes low flow velocity.[17]

Conductive heat flow was also transfered across the larger skin surface in contact with the warm water mattress (approximately 0.3–0.4 m^2). Its modest rewarming efficiency in non-cardiac surgery has been attributed to the relatively small surface available and to poor perfusion in dependent areas.[18] Although many centres currently use a circulating water mattress in adult cardiac surgery, there is no clear evidence concerning its beneficial effects in terms of heat balance when used as a sole adjuvant to core rewarming.

Nitroglycerin and high perfusion flow rates were used in all patients during systemic rewarming in order to increase heat delivery to the "cold" muscles and thereby expand the "warm" body core. Hence in the two groups pharmacological vasodilatation contributed to the attenuation in subsequent redistribution hypothermia (as heat can only flow down a temperature gradient). As reported previously by Noback and Tinker,[9] the afterdrop in nasopharyngeal temperature in control patients was related to the ratio between duration of systemic rewarming and hypothermic clamping: if systemic rewarming was prolonged >80% of clamping time, the afterdrop in nasopharyngeal temperature was attenuated. In this regard, additional skin surface warming could help to reduce the rewarming time on bypass.

TEMPERATURE AND HAEMOSTASIS

Chest fluid drainage consists of blood oozing from the surgical wound that is mixed with residual ice-slush solution and transudated fluids from the visceral pleura. An important observation was a significant correlation ($r = -0.57$) between postoperative blood loss via the chest tubes and rectal temperature on arrival in the ICU. This could explain approximately 33% of the relationship between these two variables, and the slope of the linear regression equation predicts an average additional fluid loss of 389 ml $°C^{-1}$ over a range of rectal temperatures from 37 to 34 °C. Except for the difference in rectal temperature, all other factors that would affect postoperative bleeding (i.e. activated clotting time, platelet concentration and administration of antiaggregant, nitrates and aprotinin) were similar in the two groups.

Unless considered specifically, the contribution of hypothermia to haemorrhagic diathesis is overlooked in clinical practice as standardized procedures for coagulation testing are performed at 37 °C and the number of platelets is unaffected by cold.[19] The disparity between near-normal *in vitro* clotting studies and clinically non-surgical bleeding can be attributed to both coagulation and cold-induced platelet dysfunction. First, the process of coagulation involves a series of enzymatic reactions and the speed at which these reactions occur is temperature-dependent; prothrombin and activated partial thromboplastin times are increased by approximately 10–15% when temperature decreases from 37 to 34 °C.[20 21] Second, cold-induced activation of the fibrinolytic system can further impair the haemostatic capacity, but to a much lesser extent.[22] Third, prolongation of bleeding time during mild hypothermia is caused by a defect in the ability of platelets to produce thromboxane A_2, a proaggregatory factor, at the bleeding site.[23] In heated patients, the beneficial effects of skin warming in terms of reduced bleeding were more likely attributed to better preservation of platelet function as local rewarming has been demonstrated to normalize both bleeding time and platelet aggregation.[23 24]

LIMITATIONS OF THE STUDY

In this study, extra skin warming resulted in higher rectal and nasopharyngeal temperatures in heated patients undergoing surgery of long duration with hypothermic bypass. However, we were unable to measure heat fluxes because surgical incision precluded positioning of skin temperature probes over the thorax, legs and arms. Furthermore, it is not known if extra skin warming is (more or less) beneficial during shorter surgical procedures, under normothermic conditions or in selected patients with co-morbidities (i.e. obesity, heart failure).

The amount of postoperative blood loss varies largely among different centres and reproduction of the study results depends on the adoption of similar medical management procedures. All patients were given nitroglycerin and nitroprusside which may cause impairment of lung oxygenation and exert an antiplatelet effect via increase in cyclic guanidine monophosphate and reduction of proaggregatory endoperoxide and thromboxane A_2.[25] However, nitrate-induced postoperative bleeding is questionable in the context of major surgery as high plasma concentrations of epinephrine have been shown to reverse nitrate-induced platelet inhibition.[26]

Although we observed a similar haemodynamic pattern in heated and control patients, we did not evaluate myocardial ischaemia or plasma concentrations of catecholamines which could provide a better indication of hypothermia-induced stress. Nevertheless, in the context of cardiac surgery, it is likely that activation of the sympatho-adrenal and renin–angiotensin systems, in addition to the release of vasopressin in response to surgical trauma, largely overwhelmed the mild physiological response that could be attributed to a small difference in nasopharyngeal temperature (0.8 °C).[27 28]

In summary, mild postoperative hypothermia is known to be associated with bleeding diathesis and increased oxygen demand. Our data suggest that intraoperative skin warming with a water mattress and forced warm air over the patient's face, neck and shoulders is a simple and efficient means of reducing the temperature afterdrop after hypothermic CPB and reducing postoperative blood loss. Complete rewarming of the body contributes to improved quality of perioperative care, allowing fast recovery while potentially reducing perioperative respiratory morbidity.[29] In our institution, the standard perioperative management for most cardiac surgical patients has evolved with the use of additional skin warming and short-acting anaesthetics. Such strategies are aimed at achieving earlier tracheal extubation and shorter duration of ICU stay, thereby reducing medical costs.

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Pharmacokinetics of propofol during conscious sedation using target-controlled infusion in anxious patients undergoing dental treatment

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Summary

Infusion of propofol by a target-controlled infusion (TCI) system is effective in achieving conscious sedation for anxious patients presenting for dental surgery. It is a common clinical observation that anxious patients require more anaesthetic drugs than non-anxious individuals. In study 1 we have defined blood propofol concentrations necessary for conscious sedation in both anxious ($n = 23$) and non-anxious ($n = 18$) patients. The pump performance of the TCI system, using Gepts' pharmacokinetic model, was evaluated in these two patient groups. Subsequently, clearance of propofol was compared in the two groups. Mean measured venous serum propofol concentrations obtained between 20 and 35 min after the optimal sedation level was reached were 1.6 (SD 0.2) μg ml^{-1} in the anxious patients compared with 1.7 (0.3) μg ml^{-1} in the control group (study 1) and 1.4 (0.27) μg ml^{-1} in study 2. The pump systematically overpredicted measured propofol concentrations in both groups (study 1). There was no significant difference in propofol clearance between the two groups. In study 2, an optimized set of microconstants was derived which should more accurately predict the pharmacokinetic profile of the anxious population and this set was tested prospectively in another group of 12 anxious dental patients. Bias and precision with the optimized kinetic set were significantly less than the values obtained in study 1. We conclude that there was no significant pharmacokinetic differences between anxious and non-anxious subjects receiving subanaesthetic doses of propofol for conscious sedation. (*Br. J. Anaesth.* 1998; **80**: 324–331)

Keywords: anaesthetics I.V., propofol; pharmacokinetics, propofol; surgery, dental; psychological responses

When administered in subanaesthetic doses, propofol has useful sedative and anxiolytic properties. Infusion of propofol by a target-controlled infusion (TCI) system has been shown to be effective in achieving conscious sedation for extremely anxious and mentally handicapped patients presenting for dental surgery.[1] A TCI system consists of a computer-controlled infusion pump which uses pharmacokinetic models in the calculation and delivery of infusion regimens required to theoretically achieve and maintain stable concentrations of drug in the patient.[2–5]

The first objective of this study was to define the blood propofol concentrations necessary for conscious sedation in both anxious and non-anxious patients presenting for dental chair surgery. It is a common clinical supposition that anxious patients have a greater requirement for anaesthetic drugs than non-anxious patients and we wished to establish if there was a difference between the two groups in the target concentrations at which satisfactory sedation conditions were achieved. The second objective of the study was to evaluate the performance of a target-controlled propofol infusion system using the three-compartment pharmacokinetic model proposed by Gepts and colleagues[6] during conscious sedation in these two patient groups. We subsequently analysed the relationship between measured serum propofol concentrations and the drug input regimens used by the TCI system in the two patient populations and determined and compared the clearance of propofol in the two groups. Thereafter, we derived an optimized set of microconstants which should, at least in theory, more accurately predict the pharmacokinetic profile of the anxious patient population. In a second study the performance of this refined kinetic set was tested prospectively in another 12 anxious subjects undergoing similar dental procedures (study 2).

Patients and methods

The study was approved by the Institutional Ethics Review Board of the Academic Hospital, University of Amsterdam. Children, pregnant women, patients aged more than 65 yr or ASA III or IV, or body mass index >28 kg m^{-2} were excluded from the study. Use

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Table 1 Patient characteristics (mean (SD) [range] or number)

	Study 1 Anxious patients	Study 1 Non-anxious control patients	Study 2 Anxious patients
n	23	18	12
Sex (F/M)	12/11	9/9	5/7
Age (yr)	30 [18–60]	35 [20–49]	35 [19–57]
Height (cm)	173 (9) [158–190]	174 (9) [155–189]	175 (9) [160–190]
Weight (kg)	72 (19) [68–100]	70 (9) [52–84]	78 (21) [54–128]

of concomitant medication, abuse of alcohol and allergy to propofol or soya beans were additional criteria for exclusion.

STUDY 1

We studied 23 patients (12 females, 11 males) (anxious group), ASA I or II, undergoing routine dental chair procedures. All gave informed consent to undergo the procedure under conscious sedation with propofol. These patients had been referred to the clinic because of inability to comply with dental surgery without sedation because of associated anxiety. All patients fulfilled the criteria for anxiety, as assessed using the unidimensional Corah's dental anxiety scale (DAS). DAS scores of 15–20 are an indication of anxiety[7] whereas a DAS score <10 is considered as non-anxious. A non-anxious control group (*n* = 18, nine males, nine females), undergoing extraction of one or more molars volunteered to undergo the procedure with conscious sedation. The characteristics of these two groups are shown in table 1.

No premedication was given. Articaine–epinephrine was administered for local anaesthesia when the procedure was expected to be painful. No other anaesthetic or analgesic drug was administered.

Delivery system

The TCI system was designed by one of the authors (F. E.). The program runs on a microcomputer connected to a Graseby 3400 infusion pump (Graseby Medical Ltd, Watford, UK) via an RS-232 serial interface. The computer program used a three-compartment mathematical model to calculate continuously the distribution of propofol. Pharmacokinetic microconstants derived by Gepts and colleagues[6] (table 2) were incorporated into the computerized delivery system. The initial target concentration was entered into the computer before the start of sedation. The anaesthetist could manipulate the predicted concentration in any direction at any time. Induction of sedation was achieved by rapid infusion at a rate of 700 ml h^{-1} and thereafter the computer automatically delivered an infusion regimen that was calculated to maintain the target concentration constant. Predicted blood propofol concentrations, together with the propofol infusion rate, were stored on disk every 30 s. In addition, patient number, sex, age, ASA status and weight, together with details of the infusion profile, were stored within the disk file created by the TCI pump.

Table 2 Pharmacokinetic microconstants

Study 1 Gepts and colleagues[6] Bias (%): −37.6 Precision (%): 37.7	Study 2 Optimized microconstants −5.0 16.0
V_c: 241 (litre)	V_c: 471 (litre)
K_{10}: 0.119 (min^{-1})	K_{10}: 0.0615 (min^{-1})
K_{12}: 0.114 (min^{-1})	K_{12}: 0.114 (min^{-1})
K_{13}: 0.042 (min^{-1})	K_{13}: 0.042 (min^{-1})
K_{21}: 0.055 (min^{-1})	K_{21}: 0.0375 (min^{-1})
K_{31}: 0.0033 (min^{-1})	K_{31}: 0.0033 (min^{-1})

Table 3 Sedation scale

Consciousness	Anxious patients: cooperation/treatability
1. Fully awake and oriented	Anxious, uncooperative
2. Drowsy	Mood alteration, not yet fully cooperative
3. Eyes closed, responds promptly to verbal commands	Cooperative, allows treatment to be performed
4. Eyes closed, rousable on mild physical stimulation only	
5. Eyes closed, unrousable on mild physical stimulation	

Sedation procedure

After obtaining baseline recordings of the electrocardiogram (ECG), heart rate (HR), non-invasive arterial pressure (NIAP) and oxygen saturation (Sp_{O_2}), a standardized conscious sedation regimen was initiated. An infusion of propofol with a preset target concentration of 2.5 µg ml^{-1} (study 1) was started until the patient had reached the desired clinical end-point of sedation. A five-point sedation scale was used (table 3). The aim was to reach and maintain sedation level 3. In addition, cooperation and treatability was an end-point in the anxious groups (table 3). If these clinical end-points were not reached within 3 min (inadequate sedation), the target concentration was increased, in steps of 0.2 µg ml^{-1}, until treatment could be performed. When sedation level 3 was reached, the propofol target level was maintained, unless signs of over sedation became apparent (sedation level 4), as indicated by diminished response to communication or decreasing (Sp_{O_2}). In that event the target concentration was decreased in steps of 0.2 µg ml^{-1} and the dental procedure halted temporarily until the desired sedation level was regained. When a disinhibitory type of over sedation was present (agitation, excitement, restlessness and lack of cooperation), the target concentration was decreased in the same way. Oxygen supplementation was not administered routinely. When patients were sedated adequately, a second venous access site for blood sampling for measurement of propofol concentrations was established in a large forearm vein contralateral to the site of infusion.

At the end of the dental treatment, propofol infusion was discontinued and the patient allowed to recover in the dental chair. Recovery of cognitive and psychomotor function after sedation was tested by recall of personal data and the Romberg test. When responses to these tests had returned to pre-sedation values, the patient was allowed to go home under appropriate escort.

Monitoring

NIAP was measured automatically every 5 min using a Critikon Dinamap (1846 SX) arterial pressure monitor. Heart rate and (Sp_{O_2}), were monitored continuously using a Criticare (504-US) pulse oximeter. A standard single-channel ECG was displayed on a Hewlett-Packard ECG monitor (78345A). Data collection started before sedation and continued until 5 min after discontinuation of propofol infusion. The ECG monitor, arterial pressure monitor and pulse oximeter were interfaced to a personal computer which stored on disk heart rate, systolic, diastolic and mean arterial pressures, and (Sp_{O_2}), at 30-s intervals, together with the time of recording. During the procedure, the dentist and anaesthetist continuously maintained verbal and non-verbal communication with the patient, and monitored the protective airway reflexes. The aim was to maintain sedation level 3 on the five-point sedation scale (table 3).

Venous blood sampling

Peripheral venous blood samples were obtained at the following times: 10 and 25 min after reaching the clinical end-point of sedation and at 15-min intervals thereafter. A sample was also obtained 10 min after discontinuing propofol infusion. The sampling arm was maintained at body temperature with a blanket and placed horizontally without constricting bands. No tourniquet was used during sampling. Arterial pressure was measured on the sampling arm and measurements were not performed within the 5-min period before sampling. The deadspace fluid in the cannula was removed before each sampling. Samples of blood (5 ml) were stored immediately in plain tubes at 4°C and clotted blood was centrifuged at the end of the day. Serum samples were stored at −20 °C until analysis within 30 days after collection. Propofol concentrations were assessed in duplicate by high performance liquid chromatography, as described by Plummer.[8] Accuracy of the essay was 0.48% at 2.02 $\mu g\ ml^{-1}$ and 1.46% at 4.04 $\mu g\ ml^{-1}$ The lower limit of detection was 0.025 $\mu g\ ml^{-1}$.

Computer analysis

Each measured blood concentration of propofol (C_m) was compared with the corresponding delivery system predicted target concentrations (C_P). In order to correct for the fact that the delivery performance of a TCI pump is never ideal,[9 10] the simulated concentration (C_{sim}) was calculated on the basis of the delivery system record of the infusion profile actually administered to each individual (as opposed to that which should have been given).

The percentage prediction error, calculated for each datum point was defined as:

$$\text{Prediction error } (PE_{ij}) = \frac{C_{m_{ij}} - C_{P_{ij}}}{C_{P_{ij}}} \times 100 \quad (1)$$

where $C_{P_{ij}}$ = *j*th prediction of the plasma drug concentration in the *i*th patient, and $C_{m_{ij}}$ = *j*th measurement of the plasma drug concentration in the *i*th patient.

Bias is defined as the median prediction error[11] and is a measure of the systemic tendency of the system to under or over estimate the measured concentration of blood propofol. If bias has a positive value, then the measured value is, on average, greater than the system prediction and vice versa.

$$\text{Median prediction error } (MDPE_i) = \text{median } \{PE_{ij}, j=1,\ldots, N_i\} \quad (2)$$

Precision is the median absolute performance error and is defined by:

$$(MDAPE_i) = \text{median } \{|PE_{ij}|, j=1,\ldots, N_i\} \quad (3)$$

where N_i = number of performance errors obtained in the *i*th individual.

Precision is a measure of the inaccuracy of the system.[11] Corrected values for each of the above values were calculated in an analogous manner by substituting C_{sim} for C_P. The ideal pharmacokinetic model for a delivery system produces minimum bias and precision values.[11] In order to derive a new set of pharmacokinetic variables which would more accurately predict measured blood concentrations in anxious patients, drug input and measured propofol plasma concentration data were analysed by a program (pharmacokinetic optimization (PKOPT)) that uses non-linear regression to minimize the extended least-squares objective function (NONMEM objective function (−2 log likelihood (-2LL)).[12 13] The program, developed by one of the authors (M. W.) was written in GFABasic for Windows (GFA Data Media (UK) Ltd) and runs in compiled form on an IBM 486 or a more powerful computer running either MS Windows 3.1/.11 or Windows 95. Data input is highly automated and consists of the computerized record of each infusion profile generated by the TCI pump, together with a pre-formatted file containing the measured blood propofol data. The program is capable of analysing data either from individuals or from a population (population approach). It derives a set of new population pharmacokinetic variables which significantly (by chi-square testing $P<0.01$) reduces the NONMEM objective function. The data obtained in study 1 were entered into the program, and a new set of microconstants was derived that should result in improved population bias and precision.

Clearance values of propofol for each individual in the study were calculated by obtaining the best fit to the measured propofol concentrations using the NONMEM objective function of the PKOPT program. The values thus obtained for the two patient groups were compared using the Mann–Whitney *U* test.

STUDY 2

The optimized kinetic dataset was tested prospectively in 12 highly anxious patients (five females, seven males) undergoing similar dental procedures. The target concentration was adjusted to obtain the same clinical end-point. To account for the anticipated reduced bias, the initial target concentration was set to 1.4 $\mu g\ ml^{-1}$. In study 2, venous blood samples were obtained every 15 min after patients were

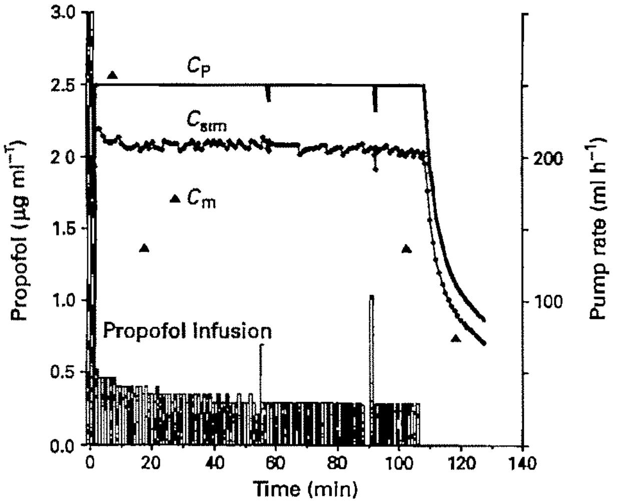

Figure 1 Course of sedation in a representative anxious female patient (aged 34 yr, weight 59 kg) The figure depicts propofol concentration predicted by the pump algorithm (C_P), the corresponding calculation based on re-simulation of the actual drug delivery profile (C_{sim}) and measured serum propofol concentrations (C_m). The increases in infusion rates at 55 and 90 min are because of replacement of a near empty syringe with a replacement filled syringe. The propofol infusion rate is also indicated.

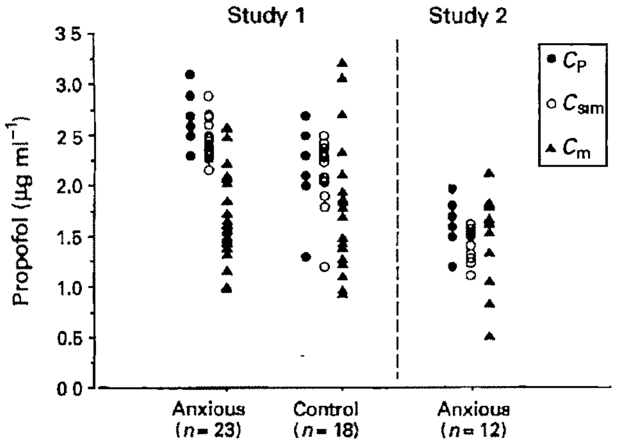

Figure 2 Propofol concentrations during conscious sedation in study 1 (anxious $n = 23$ and control $n = 18$) and study 2 (anxious $n = 12$) predicted by the pump algorithm (C_P), the corresponding calculation based on re-simulation of the actual drug delivery profile (C_{sim}) and measured serum propofol concentrations (C_m).

sedated adequately and 10 min after discontinuation of propofol infusion.

Data are presented as mean (SD), median (10th–90th percentiles) or median [range]. The pharmacokinetic performance of the various models was compared by chi-square testing of the calculated NONMEM objective functions. Probability values less than 0.05 were considered significant.

Results

STUDY 1

Figure 1 illustrates the course of sedation for a typical individual in the anxious group. An initial target of 2.5 µg ml⁻¹ was selected and, in this particular case, was deemed satisfactory for the entire course of the dental procedure. At the end of the procedure, the infusion device was turned off and the patient was allowed to recover while the predicted concentration of propofol in the patient's blood continued to be calculated by the delivery device algorithm. The measured values of serum propofol are overlaid on the system record of predicted concentration (C_P) and infusion regimen, together with the re-simulated or corrected profile based on the record of the infusion profile obtained from the pump's data file. Re-simulation revealed that the performance of the pump was less than ideal and that the corrected predicted values were somewhat less (8–10%) than those predicted by such ideal pump performance.

Table 4 Sedation data (mean (SD) [range])

	Study 1 Anxious patients	Study 2 Non-anxious control patients	Study 2 Anxious patients
Duration of infusion (min)	63 (23) [26–116]	43 (17) [25–94]	83 (37) [56–188]
Preset target propofol concentration (C_P) (µg ml⁻¹)	2.63 (0.1) [2.3–3.1]	2.4 (0.2) [1.3–2.7]	1.63 (0.1) [1.2–1.8]
Simulated blood propofol concentration (C_{sim}) (µg ml⁻¹)	2.39 (0.07) [2.1–2.84]	2.12 (0.15) [1 15–2.45]	1.36 (0.1) [1.06–1.57]
Measured serum propfol concentration (C_m) (µg ml⁻¹) at 20–35 min during optimal sedation level	1.65 (0.2) [0.93–2.52]	1.73 (0.3) [0.87–3.15]	1.42 (0.27) [0.45–2.07]
Dose rate (mg kg⁻¹ h⁻¹)	7.1 (0.8) [5.9–8.7]	7.1 (1.0) [4.5–8.7]	4.89 (1.7) [6.3–6.7]
Total dose (mg h⁻¹)	513 (167) [316–957]	490 (83) [338–658]	410 (98) [295–607]
No. of blood samples	5.7 (0.9) [4–7]	4.5 (0.9) [2–6]	5.7 (1.7) [4–9]

Sedation data are presented in table 4 and figure 2. The mean target concentration (C_P) necessary to maintain sedation level 3 in anxious patients was 2.6 (0.1) [range 2.3–3.1] µg ml⁻¹ (re-simulated values (C_{sim}) 2.4 (0.07) [range 2.1–2.8] µg ml⁻¹). Measured serum propofol concentrations (C_m) obtained between 20 and 35 min after the optimal sedation level was reached were 1.65 (0.2) µg ml⁻¹ in anxious patients compared with 1.73 (0.3) µg ml⁻¹ in the non-anxious control group. Mean duration of drug input was 63 [range 26–116] min. In the non-anxious control group, mean target concentration (C_P) at which satisfactory sedation was achieved was 2.4 (0.2) [range 1.3–2.7] µg ml⁻¹ (re-simulated values 2.12 (0.15) [range 1. 15–2.45] µg ml⁻¹). Mean duration of infusion was 43 [25–94] min. Transient over-sedation occurred in two patients in the anxious group and in three patients in the non-anxious control group.

Figure 3A shows the scatterplot of the percentage prediction errors compared with the corresponding simulated concentration for the two groups. The corrected median prediction error (bias) calculated for the anxious population was −32.4% compared with −22.2% in the non-anxious control group. Precision was 33.7% in the anxious population and 28.3% in the non-anxious control group. Therefore, in both groups the pump systematically overpredicted measured propofol concentrations. The time related course of prediction error for each individual in the

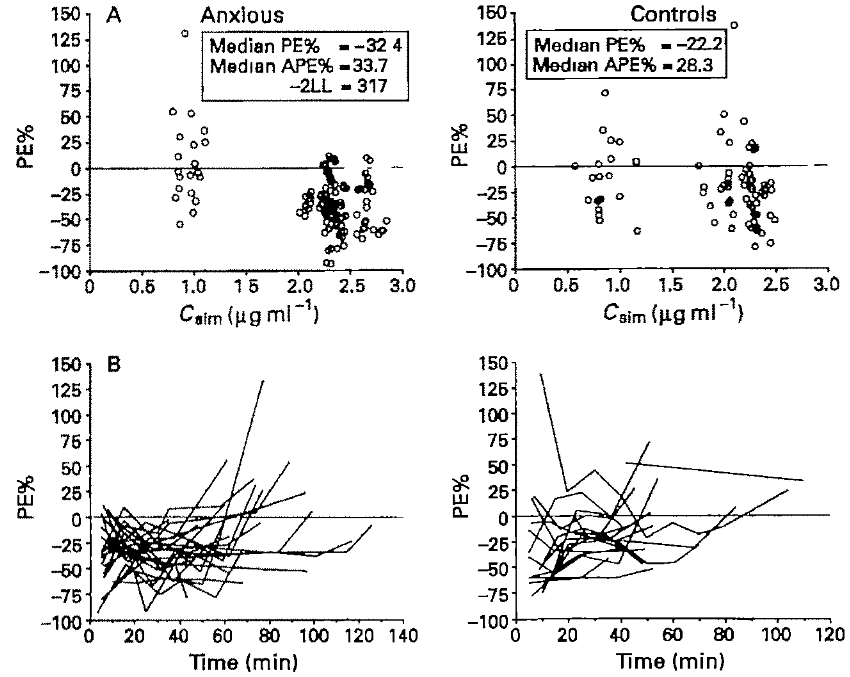

Figure 3 A: Percentage prediction error (PE%) *vs* predicted propofol concentration (C_{sim}) based on re-simulation using the actual amount of propofol and the pharmacokinetic microconstants published by Gepts and colleagues[6] delivered by the TCI system in anxious and control patients. B: Percentage prediction error (PE%) *vs* time for each patient in the anxious and control groups.

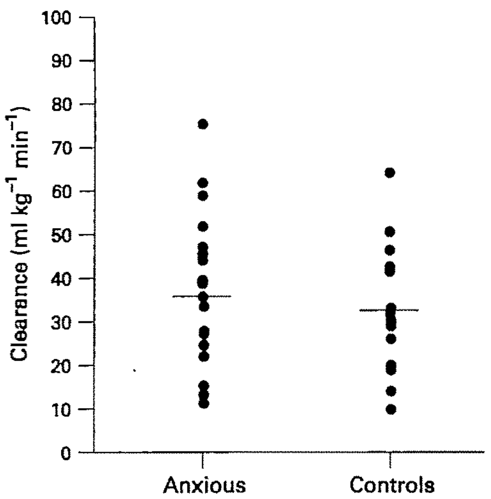

Figure 4 Individual propofol clearance values in the anxious and control patients (study 1) determined by obtaining the best fit to the measured propofol concentrations using the NONMEM objective function of the PKOPT program. Horizontal bars indicate median values.

two groups is shown in figure 3B. There was no significant difference in propofol clearance between the two groups (fig. 4). Median clearance was 36.0 (11.9–62.1) ml kg^{-1} min^{-1} in anxious patients and 31.7 (13.9–50.5) ml kg^{-1} min $^{-1}$ in non-anxious control subjects.

STUDY 2

The data obtained from the anxious group in study 1 were entered into the PKOPT program and a new set of population microconstants (table 2) was derived which significantly minimized ($P < 0.01$) the NONMEM objective function for the experimental data from study 1 and which should result in improved pump performance. For each measurement of blood propofol a new prediction error was calculated on the basis of a new predicted value based on the new pharmacokinetic model derived by the computer program. The values of bias and precision calculated on the basis of the new optimized model were 0.02 and 25%, respectively (fig. 5A) The NONMEM objective function (−2LL) was reduced from 317 to 195. No additional improvement in the objective function was obtained by an additional regression step to include patient age.

The refined microconstants were then used to update the TCI pump delivery program and both the clinical and pharmacokinetic performance of this system were assessed prospectively in a second group of 12 patients. The clinical data are shown in table 4. No oversedation was encountered with the modified pharmacokinetic settings in any patient. The target propofol concentration in study 2 necessary to maintain sedation level 3 was 1.6 (0.1) [range 1.1–1.9] μg ml^{-1} (re-simulated values 1.36 [range 1.06–1.57] μg ml^{-1}) (fig. 2). Mean duration of propofol delivery was 83 (37) [range 56–188] min. Measured serum propofol concentration obtained between 20 and 35 min after reaching the optimal sedation level was 1.42 (0.27) μg ml^{-1}. The time course of pump predictive performance is shown in figure 5B. Median prediction error (bias) after re-simulation was −5.0% and precision was 16%. Bias and precision with the optimized kinetic set were significantly ($P < 0.01$) less than the values obtained in study 1. A mean of 2 (range 0–3) alterations in target concentrations were made in all patients.

In all patients, haemodynamic and (Sp_{O_2}), indices were stable and there were no instances of deviation greater than 15% from baseline.

Discussion

In study 1, the measured serum propofol concentration necessary to maintain the optimal level of sedation in our study was approximately 1.5 μg ml^{-1}, and

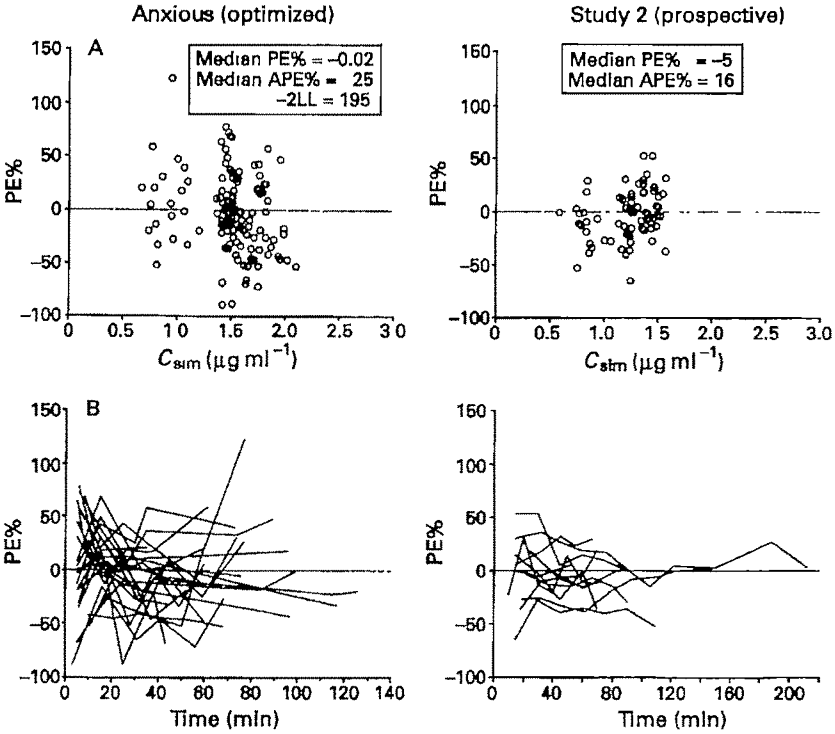

Figure 5 A: Percentage prediction error (PE%) *vs* predicted propofol concentration (C_{sim}) based on re-simulation using the actual amount of propofol delivered and the optimized pharmacokinetic microconstants derived with PKOPT program in anxious patients from study 1 and anxious patients in the prospective study 2. B: Percentage prediction error (PE%) *vs* time for each individual, using the optimized pharmacokinetic microconstants derived with the PKOPT program in anxious patients from study 1 and anxious patients in the prospective study 2.

there were no significant differences between anxious and non-anxious control patients. In study 2, similar serum propofol concentrations were measured in anxious patients using the optimized kinetic data set, despite lower target concentrations being set on the modified TCI system. The results of study 1 revealed no evidence to support the existence of a difference in propofol clearance between anxious patients and non-anxious controls.

For study 1, in both anxious and non-anxious subjects receiving subanaesthetic doses of propofol via a target-controlled infusion system using Gepts' kinetic dataset, measured values of propofol were systematically overestimated by the delivery system model. The clinical setting in which Gepts' microconstants were derived[6] differed considerably from the conditions in our study involving dental outpatients, and these differences may partly explain the large negative bias observed in our study. Gepts' parameter set was derived from three groups of six patients who were older than the dental patients and volunteer subjects in our study. Propofol was administered as a constant rate infusion for at least 2 h at a rate of 3 μg ml^{-1} h^{-1} in patients aged approximately 60 yr, 6 μg ml^{-1} h^{-1} in patients aged 50 yr and 9 μg ml^{-1} h^{-1} in patients aged 40 yr, who underwent urological procedures under spinal or local anaesthesia. The infusion rates necessary to maintain conscious sedation in our dental patients and volunteers were of the order of 4.5–8.7 μg ml^{-1} h^{-1}. Lastly, in Gepts' analysis, arterial sampling was performed, whole blood samples were collected and whole blood propofol concentrations were determined whereas in our study, sampling was from a venous site and serum propofol concentrations were measured.

We opted to obtain venous samples to minimize discomfort and risk in our highly anxious patients. The decision to use venous rather than arterial blood samples may have resulted in lower measured blood propofol concentrations compared with Gepts' study. During a bolus and infusion regimen that achieves and maintains a constant arterial concentration, it may be expected that the AV differences are greatest initially as drug is distributed rapidly into the tissues. This difference diminishes as the tissues become saturated, until after some minutes arterial and venous concentrations are the same. Chiou[14] demonstrated that at steady state during constant infusion, there was no difference in arterial and venous blood (plasma) concentrations during the dosing interval as peripheral tissue uptake of propofol is zero. Coetzee and colleagues[15] suggested that in evaluating propofol TCI, it is preferable to use arterial concentrations, but venous concentrations can be used too, bearing in mind that propofol venous concentrations are lower than arterial values and that sampling should be performed several minutes after adjustment to the targeted concentration. Because we obtained venous blood 10 min after reaching the clinical end-point of sedation (at least 15 min after the start of infusion), it is unlikely that the difference between arterial and venous blood propofol concentrations was sufficient to explain the observed negative bias. We have determined propofol concentrations in serum. Propofol concentrations in whole blood, plasma or serum may differ. Coetzee and colleagues[15] compared propofol concentrations in whole blood, plasma and serum in 65 samples obtained from 10 patients, with propofol concentrations in the range 0.5–7.5 μg ml^{-1}. Propofol concentrations in whole

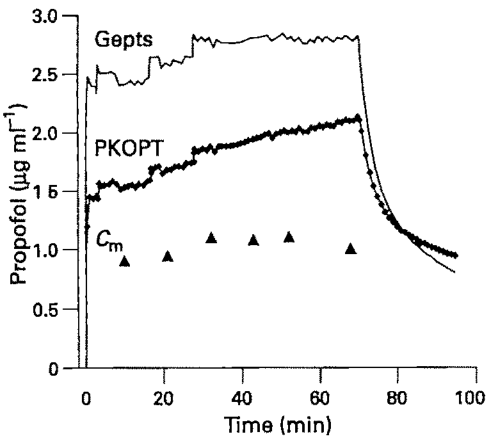

Figure 6 Predicted and measured serum propofol concentrations in one anxious patient receiving a target-controlled propofol infusion using a pump programmed with the pharmacokinetic microconstants published by Gepts and colleagues[6] and time course of theoretical blood propofol concentrations after re-simulation using the optimized microconstants from the PKOPT program. C_m = measured serum propofol concentration.

blood were, on average, 0.3 μg ml^{-1} higher than in serum, and there were no significant differences between concentrations in plasma and serum. The authors concluded that the differences were not large enough to influence the concentrations achieved and the prediction errors.[15] It is possible that part of the observed difference between predicted and measured propofol concentration in our study can be attributed to the difference in blood propofol determination between our study and that of Gepts' (whole blood).

In both the anxious and non-anxious groups in our study, over prediction of the delivery system model (Gepts) diminished with time such that after approximately 60 min of infusion time the model tended rather to under predict the measured concentrations than vice versa. This observation suggests that, in the context of the present study, the use of the Gepts' model in the delivery system produced an inherent tendency to drift towards a deeper level of sedation despite the pump settings remaining constant. The reason for this is apparent from figure 6. This illustrates the results of a computer simulation of predicted propofol concentrations in one of the study 1 patients receiving propofol from the TCI system programmed with Gepts' kinetic set, but projected instead into the new model derived by the optimization program. It can be seen that the predicted propofol concentrations according to the new model are initially substantially lower than those predicted by the Gepts' model but progressively increase during the course of the infusion. The refined model derived by the optimization program successfully eliminated this problem and produced a stable time relationship between measured and predicted values.

Hepatic extraction of propofol is high and clearance is dependent on liver blood flow.[15] Propofol has been shown to decrease cardiac output in a dose-dependent manner in humans, which in turn may dynamically influence propofol kinetics by reducing the rate of distribution to peripheral tissues and thereby contributing to a reduction in hepatic blood flow. It is conceivable that the higher age of Gepts' patients, possibly combined with reduction in cardiac output or hepatic blood flow, or both, may have resulted in lower values for propofol clearance than were observed in our study. The substantial negative bias observed in our sedation study was predicted by Coetzee and colleagues[15] who proposed that the clearance of propofol is concentration dependent. Clearance and distribution of the drug were postulated to occur at a faster rate at lower concentrations. Thus a pharmacokinetic study performed at higher concentrations would produce slower kinetics than one performed at a lower concentration. The results of our study support the hypothesis that the pharmacokinetics of propofol are concentration dependent.

Skipsey and colleagues[16] reported in a study involving older patients undergoing orthopaedic procedures under regional anaesthesia that their patients were satisfactorily sedated at a mean blood propofol concentration of 1.05 [range 0.15–2.63] μg ml^{-1}. Our findings are in accordance with their statement that patients with a blood propofol concentration of approximately 1–1.5 μg ml^{-1} are sedated but respond to verbal stimulation. This appeared to be true both in anxious patients and non-anxious control subjects.

The main purpose of a TCI pump is to produce a stable blood concentration of the delivered drug which is as close as possible to that predicted by the delivery system algorithm. The pharmacokinetic performance of any TCI system is thus highly dependent on how well the applied pharmacokinetic data in the delivery program match the characteristics of the target population. Inter- and intra-patient variability, variable intraoperative haemodynamic states and changing surgical stimulus contribute to considerable variability in pump performance in clinical practice. In the context of conscious sedation, the appropriateness of the pharmacokinetic delivery system model is particularly important because the therapeutic range for sedation is much smaller than for general anaesthesia. Our study demonstrated that the 10–90 percentile range predicted target concentration selected for conscious sedation in anxious patients was 2.11–2.65 μg ml^{-1} whereas the corresponding range for general anaesthesia is 2–10 μg ml^{-1}.[17] Relatively small prediction errors result in over or under sedation.

One of the main objectives of this study was to derive a new set of pharmacokinetic constants which more accurately described the elimination of propofol in anxious patients undergoing conscious sedation. The optimized model produced significantly ($P<0.01$) improved pharmacokinetic performance compared with the original system using the pharmacokinetic microconstants derived by Gepts and colleagues[6] and this result could be confirmed in a prospective study. The new model also demonstrated improved time related performance producing accurate and stable concentrations of propofol over a time period of up to 2 h.

Acknowledgements

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British Journal of Anaesthesia 1998; 80: 332–336

Positive pressure ventilation with the laryngeal mask airway in non-paralysed patients: comparison of sevoflurane and propofol maintenance techniques

C. KELLER, H. J. SPARR AND J. R. BRIMACOMBE

Summary

We have compared anaesthetic maintenance and emergence characteristics of propofol and sevoflurane with the laryngeal mask airway (LMA) at commonly used doses in 185 ASA I–II patients, in a randomized, prospective study. Anaesthesia was induced with propofol 2.5–3.5 mg kg^{-1} and fentanyl 1–3 μg kg^{-1}. Neuromuscular blocking agents were not used. All patients underwent positive pressure ventilation (PPV) with tidal volumes of 6–8 ml kg^{-1} to maintain normal end-tidal carbon dioxide concentration. Anaesthesia was maintained with 66% nitrous oxide in oxygen and infusion of propofol 6 or 8 mg kg^{-1} h^{-1}, or 1% or 1.5% end-tidal sevoflurane. There were no failed insertion attempts and adequate ventilation was achieved in all patients. During emergence, there was a greater incidence of excitatory phenomena with 1% and 1.5% sevoflurane (95% confidence intervals (CI) 4–19%) compared with propofol (95% CI 0–4%). Sevoflurane 1.0% (95% CI 37–71%) was associated with the greatest overall incidence of respiratory and haemodynamic problems. This was significantly higher compared with propofol 6 mg kg^{-1} h^{-1} (95% CI 19–36%). Shorter times to LMA removal were observed with 1% and 1.5% sevoflurane compared with propofol ($P<0.0002$). Postoperative problems did not differ between groups. We conclude that propofol 6–8 mg kg^{-1} h^{-1} and 1.5% sevoflurane were suitable for maintenance of anaesthesia for musculoskeletal surgery in non-paralysed ASA I–II patients undergoing PPV with the LMA. Emergence was more rapid with sevoflurane, but was associated with more excitatory phenomena. (*Br. J. Anaesth.* 1998; **80**: 332–336)

Keywords: equipment, masks anaesthesia; ventilation, positive pressure; anaesthetics volatile, sevoflurane; anaesthetics i.v., propofol

Propofol is becoming increasingly popular for maintenance of anaesthesia, particularly for ambulatory surgery,[1] and sevoflurane is an acceptable alternative.[2-4] Both agents allow rapid changes in anaesthetic depth, a favourable emergence profile and minimal postoperative morbidity. Studies have compared propofol with sevoflurane anaesthesia in paralysed patients with the trachea intubated, and shown them to be similar in terms of cardiorespiratory effects, emergence times and adverse events.[2-4]

The laryngeal mask airway (LMA) has gained widespread acceptance as a general purpose airway, with usage rates of up to 30%.[5] Large scale studies (total 18 410 patients) suggest it is safe and effective for spontaneous ventilation (8139 patients) and positive pressure ventilation (10 271 patients).[5-7] The LMA offers several advantages over the tracheal tube, including improved haemodynamic stability, reduced anaesthetic requirements for airway tolerance, lower frequency of coughing, improved oxygen saturation during emergence and less sore throat,[8] and does not require neuromuscular block. Although both propofol[9] and sevoflurane[10] have been used for maintenance of anaesthesia with the LMA, there have been no comparative studies evaluating their clinical efficacy.

In this randomized study, we have compared maintenance and emergence characteristics of sevoflurane–nitrous oxide with propofol–nitrous oxide anaesthesia at commonly used doses in non-paralysed patients undergoing ventilation with the LMA.

Patients and methods

This study was approved by the Research and Ethics Committees of the University Hospital of Innsbruck and written informed consent was obtained from all patients. We studied 185 consecutive patients undergoing musculoskeletal surgery expected to last more than 30 min in the supine position, allocated randomly to one of four treatment groups. In groups I and II anaesthesia was maintained with 66% nitrous oxide in oxygen and infusion of propofol 6 or 8 mg kg^{-1} h^{-1}, respectively. In groups III and IV anaesthesia was maintained with 66% nitrous oxide in oxygen and either 1% or 1.5% end-tidal sevoflurane, respectively. Sample size was based on the need to show a 20% difference in orientation time between groups, with a type I error of 0.05 and a power of 0.8.

Patients were excluded if they were less than 19 or more than 65 yr of age, ASA III–V, had a history of malignant hyperthermia, respiratory tract pathology, a sore throat within 10 days, known difficult airway,

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body mass index greater than 30 kg m^{-2} or were at risk of regurgitation/aspiration (previous upper gastrointestinal tract surgery, known or symptomatic hiatus hernia, oesophageal reflux, peptic ulceration or not fasted).

Patients were allocated randomly to treatment groups by opening sealed envelopes, 1–2 h before operation. Anaesthesia was standardized. Premedication comprised midazolam 7.5 mg orally approximately 1 h before induction. Monitoring was started before induction of anaesthesia and included ECG, pulse oximetry, capnography and non-invasive arterial pressure. Oxygen was given by face mask and then fentanyl 1–3 μg kg^{-1} was given followed 1 min later by propofol 2.5–3.5 mg kg^{-1} over 30 s. Immediately before insertion, the LMA was lubricated with saline. No attempt was made to ventilate the patient's lungs via a face mask or to instrument the airway with suction catheters at any time during anaesthesia. The LMA was inserted 30 s after completion of the bolus dose of propofol using the standard recommended insertion technique,[11] with the cuff deflated and the rim facing posteriorly when the eyelash reflex was lost and the jaw relaxed. A size 3 LMA was used for patients weighing 30–60 kg and a size 4 for patients more than 60 kg (size 5 LMA was unavailable during the study). Additional bolus doses of propofol 0.5 mg kg^{-1} were given as required until an adequate level of anaesthesia was achieved for placement. All LMA were inserted by a single experienced user (C. K.) (more than 800 previous placements). The cuff was initially inflated with 20 ml of air in the size 3 and 30 ml in the size 4. Successful placement was judged by chest wall movement and capnography during manually assisted ventilation. After successful placement, the LMA was fixed in place in the midline with the tube following its natural caudal curve using adhesive tape.[11] A wad of gauze swabs rolled into a cylindrical shape was placed alongside the LMA to function as a bite block.[11] Cuff pressures were monitored throughout the procedure using a calibrated aneroid manometer (Mallinckrodt Medical, Athlone, Ireland) which was attached to the pilot balloon. Cuff pressures were maintained at less than 60 cm H_2O by intermittently withdrawing gas from the cuff. Patients underwent positive pressure ventilation (PPV) with tidal volumes of 6–8 ml kg^{-1} and peak airway pressures were limited to 15 cm H_2O. Ventilatory frequency was adjusted to maintain end-tidal carbon dioxide in the normal range (4.4–5.3 kPa).

Anaesthesia was maintained with 66% nitrous oxide in oxygen and propofol 6 or 8 mg kg^{-1} h^{-1}, or 1.0% or 1.5% end-tidal sevoflurane. Airway gases were sampled from the proximal end of the LMA. A circle anaesthetic breathing system was used and there was no active humidification in the anaesthesia system. Fresh gas flows were 2 litre min^{-1} of oxygen and 4 litre min^{-1} of nitrous oxide. Depth of anaesthesia was assessed by observing ventilatory frequency, patient movement, heart rate and arterial pressure and, if considered inadequate, fentanyl 1 μg kg^{-1} was given. If coughing, retching or laryngospasm occurred, propofol 0.5 mg kg^{-1} was given. The maintenance dose of propofol or sevoflurane was continued until completion of surgery. Emergence took place in the operating room in the supine position with the patient undisturbed and breathing 100% oxygen. LMA removal time was determined by asking the patient in a normal tone of voice to open his or her eyes and mouth. This was repeated every 15–30 s until both appropriate responses were obtained. The LMA and bite block were removed simultaneously and the time recorded. Orientation time was determined by asking the patient in a normal tone of voice to state his or her name and date of birth. This was repeated every 15–30 s until a correct response was obtained and the time recorded.

Patient data, including sex, age, weight, smoking history and duration of surgery were recorded for each patient. In addition to the standard anaesthetic record, mean arterial pressure (MAP) and heart rate (HR) were recorded before induction, every minute from induction to incision, every 5 min after incision, and every minute after anaesthesia was discontinued until the LMA was removed. Problems during induction and surgery were documented by the anaesthetist (C. K.) not blinded to the type of anaesthetic. Problems during emergence and in the postoperative period were recorded by an anaesthetist (H. S.) blinded to the type of anaesthetic. Problems were classified as respiratory, haemodynamic or excitatory phenomena. Respiratory problems included failed insertion attempt (failed placement within 20 s), failed ventilation (failure to maintain Pa_{CO_2} within the normal range or Sp_{O_2} <95% with FI_{O_2}>33%), coughing, retching, hiccup, laryngospasm (a sudden increase in peak airway pressure greater than 25 cm H_2O), bronchospasm, regurgitation, aspiration, gastric insufflation (air heard entering the stomach on auscultation over the epigastrium), increased salivation, biting and any other untoward airway event. Haemodynamic problems included hypertension/hypotension, tachycardia/bradycardia and other arrhythmias. Hypertension or hypotension was defined as MAP±20% of preinduction baseline values, respectively. Tachycardia or bradycardia was defined as heart rate greater that 100 beat min^{-1} or less than 60 beat min^{-1}, respectively. Excitatory phenomena included inco-ordinate movement, shivering and straining. Successful induction, maintenance and emergence were defined as the absence of any respiratory or cardiovascular problems during that time. Anaesthesia was divided into three phases: induction (start of anaesthesia until successful placement of the LMA); maintenance (successful placement of the LMA until anaesthesia discontinued) and emergence (anaesthesia discontinued until patient orientated). Time intervals recorded included anaesthesia time (start of anaesthesia until anaesthesia discontinued), LMA removal time (anaesthesia discontinued until LMA removed) and orientation time (anaesthesia discontinued until patient orientated).

Each patient underwent a structured interview (H. S.) 18–24 h after surgery during which they were asked about postoperative hoarseness (yes/no), nausea (yes/no) and vomiting (yes/no). Sore throat was graded by the patient as none (no sore throat at any time since the operation), mild (sore throat disappeared within 6 h), moderate (sore throat disappeared within 12 h) and severe (sore throat lasted 12 h or more).

Data were analysed with the Student's *t* test and chi-square test using the software package SPSS

Table 1 Patient and anaesthetic characteristics in the four groups (mean (SD or range) or number)

	Propofol		Sevoflurane	
	Group I 6 mg kg^{-1} h^{-1}	Group II 8 mg kg^{-1} h^{-1}	Group III 1.0%	Group IV 1.5%
n	47	48	45	45
Age (yr)	39 (19–64)	37 (20–60)	37 (22–61)	39 (19–63)
Height (cm)	171 (9)	173 (9)	172 (9)	171 (9)
Weight (kg)	69 (12)	71 (13)	70 (12)	72 (12)
Body mass index (kg m^{-2})	23 (3)	24 (3)	24 (3)	24 (3)
Sex M/F (*n*)	26/21	28/20	24/21	25/20
ASA I/II (*n*)	40/7	38/10	40/5	38/7
Smoking history (*n*)	10	14	12	12
Anaesthesia time (min)	48 (22)	53 (27)	51 (25)	54 (21)
Min. to max. anaesthesia time (min)	30/90	30/110	35/120	35/105
Procedures (*n*)				
Knee	28	33	35	30
Foot and ankle	12	10	6	10
Hand and shoulder	7	5	4	5
Propofol induction dose (mg kg^{-1})	3.0 (0.3)	3.0 (0.4)	3.0 (0.4)	3.0 (0.3)
Fentanyl induction dose (μg kg^{-1})	1.8 (0.5)	1.9 (0.6)	1.9 (0.4)	1.9 (0.4)
Additional intraoperative drugs (*n*)				
Fentanyl (1 μg kg^{-1})	3	5	5	2
Propofol (0.5 mg kg^{-1})	0	0	4	0
Atropine (0.5 mg)	7	6	8	6
Emergence times (min)				
LMA removal	8.0 (2.4)	9.1 (2.8)	6.1 (2.4)	6.5 (2.1)
Orientation	14.5 (4.8)	15.3 (5.0)	9.7 (3.3)	9.1 (3.67)

Table 2 Respiratory, haemodynamic and postoperative problems during each phase of anaesthesia (number (%))

	Propofol		Sevoflurane	
	Group I 6 mg kg^{-1} h^{-1}	Group II 8 mg kg^{-1} h^{-1}	Group III 1.0%	Group IV 1.5%
n	47	48	45	45
Minimal Sp_{O_2} (%)	96	95	96	96
Induction				
Hiccup	1 (2%)	2 (4%)	0 (0%)	0 (0%)
Hypotension	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Bradycardia	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Maintenance				
Laryngospasm	0 (0%)	0 (0%)	4 (9%)	0 (0%)
Hypotension	0 (0%)	3 (6%)	0 (0%)	1 (2%)
Hypertension	2 (4%)	3 (6%)	4 (9%)	1 (2%)
Bradycardia	9 (19%)	10 (21%)	12 (27%)	10 (22%)
Emergence				
Cough	0 (0%)	2 (4%)	4 (9%)	0 (0%)
Retching	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Increased salivation	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Biting	4 (9%)	5 (10%)	7 (16%)	8 (18%)
Hypertension	1 (2%)	0 (0%)	2 (4%)	2 (4%)
Excitement	0 (0%)	0 (0%)	4 (9%)	5 (11%)
Postoperative				
Mild sore throat	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Hoarseness	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nausea	1 (2%)	0 (0%)	1 (2%)	3 (7%)
Vomiting	0 (0%)	0 (0%)	0 (0%)	1 (2%)

(version 6.0 for Windows, SPSS Inc., Chicago, IL, USA). Significance was taken as $P<0.05$.

Results

There were no significant differences between the four groups in age, weight, height, body mass index, ASA status, sex distribution, smoking history, type of surgical procedure, anaesthesia time, administration of adjunctive drugs and induction doses of fentanyl and propofol (table 1).

Problems occurring during the three phases of anaesthesia are given in table 2. There were no failed insertion attempts and adequate ventilation was achieved in all patients. The lowest oxygen saturation recorded during the study was 95%. There were no episodes of gastric distension, regurgitation, aspiration or bronchospasm. The incidence of problems at induction was similar in all groups. During maintenance, the incidence of laryngospasm and requirements for additional propofol were greater with 1% sevoflurane (95% confidence intervals (CI) 2–23%) compared with 1.5% sevoflurane (95% CI 0–8%) or the propofol groups (95% CI 0–7%). During emergence, there was a greater incidence of excitatory phenomena with 1% and 1.5% sevoflurane (95% CI 4–9%) compared with propofol (95% CI 0–4%).

HR (fig. 1) and MAP (fig. 2) for each group were similar during induction and maintenance of anaesthesia. There was no haemodynamic stress response to placement of the LMA. During emergence, HR was greater with sevoflurane at 3–7 min after discontinuation of anaesthesia ($P<0.05$). MAP was similar.

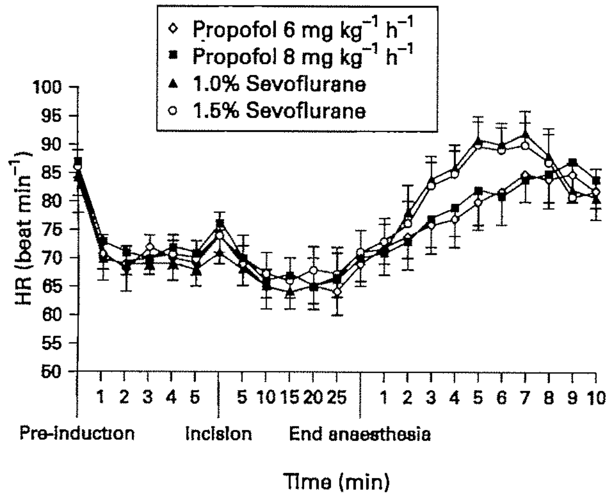

Figure 1 Heart rate (HR) before induction of anaesthesia, at the indicated times after induction, at skin incision, at the indicated times after skin incision, at the end of administration of anaesthesia and at the indicated times after anaesthesia in the four treatment groups (mean (SD)). HR was significantly greater with sevoflurane at 3–7 min after discontinuation of anaesthesia.

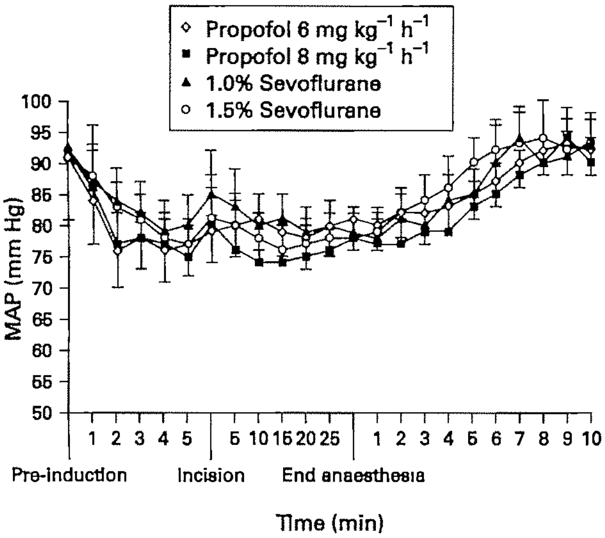

Figure 2 Mean arterial pressure (MAP) before induction of anaesthesia, at the indicated times after induction, at skin incision, at the indicated times after skin incision, at the end of administration of anaesthesia and at the indicated times after anaesthesia in the four treatment groups (mean (SD)). There were no significant differences between groups.

The total number of patients with respiratory and haemodynamic problems during each phase of anaesthesia is given in table 3. Sevoflurane 1.0% (95% CI 37–71%) was associated with the greatest overall incidence of respiratory and haemodynamic problems. This was significantly higher compared with propofol 6 mg kg^{-1} h^{-1} (95% CI 19–36%), but there were no other significant differences between groups. Significantly shorter times to LMA removal and orientation were observed with 1% and 1.5% sevoflurane compared with propofol 6 and 8 mg kg^{-1} h^{-1} ($P<0.0002$). Removal and orientation times were similar for 1% sevoflurane compared with 1.5% sevoflurane, and similar for propofol 6 and 8 mg kg^{-1} h^{-1}. Postoperative problems did not differ between groups. The incidence of sore throat was 2.7% and hoarseness 0%. The number of patients who received postoperative analgesia was similar between groups.

Discussion

Our data suggest that maintenance of anaesthesia with propofol 6–8 mg kg^{-1} h^{-1} or 1.5% sevoflurane in nitrous oxide provides satisfactory anaesthetic conditions in non-paralysed patients undergoing ventilation with an LMA. Sevoflurane 1.0% provided less satisfactory conditions and this was probably related to inadequate depth of anaesthesia. The overall incidence of problem-free maintenance and emergence was similar to that reported in paralysed patients whose tracheas were intubated,[3] but randomized controlled studies are required to determine if either technique offers an advantage.

During induction and maintenance of anaesthesia, haemodynamic variables were similar. This contrasts with the results of Fredman and colleagues who showed slower heart rates in the immediate post-induction period in paralysed patients whose tracheas were intubated.[2] The reason for this difference is not clear. During emergence, heart rate was greater with sevoflurane. MAP was similar in all groups during emergence. The high incidence of bradycardia in all groups may reflect the lack of cardiovascular stimulation resulting from the LMA.

The efficacy of the LMA technique for PPV is already established, but most controlled studies involve paralysed patients.[7] [12–15] Our data suggest that the technique is also suitable for non-paralysed patients. It is interesting that, despite cuff pressure limitation to 60 cm H_2O, in all patients ventilation was adequate using tidal volumes of 6–8 ml kg^{-1} and peak airway pressures of 15 cm H_2O. This may be related to the relatively low body mass index of the study population (BMI <30 kg m^{-2}) and accurate placement of the device. Dyer, Llewellyn and James have shown the LMA to be an effective device for PPV using total i.v. anaesthesia with propofol and easier to manage than the tracheal tube in the absence of neuromuscular blockers.[9]

The times required for LMA removal and orientation were shorter with sevoflurane. These times

Table 3 Incidence of respiratory and haemodynamic problems during each phase of anaesthesia (number (%))

	Propofol		Sevoflurane	
	Group I 6 mg kg^{-1} h^{-1}	Group II 8 mg kg^{-1} h^{-1}	Group III 1.0%	Group IV 1.5%
n	47	48	45	45
Induction	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Maintenance	10 (21%)	12 (25%)	16 (36%)	11 (24%)
Emergence	5 (11%)	8 (17%)	13 (29%)	11 (24%)
Total	14 (30%)	18 (37%)	25 (56%)	19 (42%)

were similar to those reported for sevoflurane and propofol in paralysed patients whose tracheas were intubated.[2 3] The highest incidence of nausea (7%) and vomiting (2%) was in the 1.5% sevoflurane group, but this was not significantly different from the other groups. The incidence of nausea and vomiting was 2–10 times less than previously reported for paralysed patients whose tracheas were intubated[5] and may reflect different methods of data collection, different types of surgery or antiemetic therapy. It would seem unlikely that this was related to the LMA as previous studies have reported a similar incidence of postoperative nausea and vomiting when comparing the LMA with the tracheal tube.[16 17] No routine intraoperative antiemetic was given in our study and there was no case of gastric insufflation.

The incidence of sore throat with the LMA is approximately 10%, but varies between 0 and 50%,[18–23] and the incidence of hoarseness is approximately 4%.[21–24] The incidence of sore throat and hoarseness in our study was low (2.7% and 0%, respectively). This probably reflects the high first time placement rate, use of standard insertion technique and adoption of low intra-cuff pressures. All LMA were inserted by an experienced user with more than 800 previous placements. It has been shown that there are short-term (>75 uses)[25] and long-term (>750 uses)[6] learning curves with the LMA. Burgard, Mollhoff and Prien demonstrated that reducing cuff pressure to the minimum required for an adequate seal produced a reduction in sore throat from 8 to 0%.[22] The 13% incidence of biting during emergence highlights the importance of using a bite block with the LMA.

We conclude that propofol 6–8 mg kg^{-1} h^{-1} and 1.5% end-tidal sevoflurane were suitable for maintenance of anaesthesia for musculoskeletal surgery in non-paralysed ASA I–II patients undergoing PPV with the LMA. Emergence was more rapid with sevoflurane, but was associated with more excitatory phenomena and tachycardia.

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British Journal of Anaesthesia 1998; **80**: 337–341

Catheter deadspace: a source of error during tonometry

P. J. G. M. STEVERINK, J. J. KOLKMAN, A. B. J. GROENEVELD AND J. W DE VRIES

Summary

Tonometry of $P\text{co}_2$ is a promising method for assessing the oxygen supply to demand ratio of the gastrointestinal mucosa in critically ill patients. A balloon-tipped tonometer is introduced into the stomach or sigmoid colon, and saline is instilled into the balloon. After a time to allow partial equilibration with intraluminal $P\text{co}_2$, saline is aspirated and $P\text{co}_2$ is measured. Intermittent instillation and aspiration of saline allows serial $P\text{co}_2$ measurements, provided correction factors are used to calculate the $P\text{co}_2$ value expected at full equilibration from the $P\text{o}_2$ values measured after short dwell times. The technique is not yet widely applied, partly because of methodological controversies. We evaluated the role of the catheter deadspace as a source of error during $P\text{co}_2$ tonometry. The increase in $P\text{co}_2$ in sigmoid-type tonometers with a normal length (normal tonometer (NT)) and in those with a 50% increase in length and thus deadspace (extended tonometer (ET)), in a saline bath at a $P\text{co}_2$ of 4.8 kPa was assessed. Saline dwell times were 10, 20, 30, 45, 60 and 90 min and the time-dependent $P\text{co}_2$ increase was determined at deadspace $P\text{co}_2$ values of approximately 4.0 and 8.0 kPa following contamination of the catheter deadspace after immersion in saline baths at $P\text{co}_2$ values of 4.8 and 9.6 kPa, respectively, before each measurement cycle. In another experiment, the tonometer was rinsed between measurement cycles to remove deadspace saline containing carbon dioxide and to obviate contamination of instilled saline. $P\text{co}_2$ was measured in a blood-gas analyser, taking into account measurement bias in saline. Failure to remove deadspace saline between measurement cycles resulted in an overestimation of 10% and 6% for the NT and 16% and 10% for the ET, at saline dwell times of 10 and 20 min, respectively, at a deadspace $P\text{co}_2$ of approximately 4.0 kPa. At a deadspace $P\text{co}_2$ of approximately 8.0 kPa, $P\text{co}_2$ was overestimated by 17%, 11% and 5% for the NT and 31%, 20% and 11% for the ET, at dwell times of 10, 20 and 30 min, respectively. Rinsing the NT/ET resulted in accurate assessment of $P\text{co}_2$ at all dwell times, but the dwell time-dependent increase in $P\text{co}_2$ was slightly slower in the ET, particularly at 10 min, after a sink effect of the increased deadspace. Hence, a previously unrecognized deadspace effect caused error during $P\text{co}_2$ tonometry, particularly with short dwell times. This potentially large error can be avoided by rinsing the tonometer before each measurement cycle, allowing accurate $P\text{co}_2$ tonometry even at 10-min saline dwell times, provided that correction factors are used that are specific for catheter size. These findings may help to widen the clinical applicability of tonometry. (*Br. J. Anaesth.* 1998; **80**: 337–341)

Keywords: carbon dioxide, partial pressure; airway, deadspace; monitoring, tonometry

The tonometry of intraluminal $P\text{co}_2$ in the gastrointestinal tract and calculation of intramucosal pH may be useful in assessing the prognosis and guiding treatment of critically ill patients.[1–8] During tonometry, saline instilled into the tonometer balloon is allowed to equilibrate with intraluminal $P\text{co}_2$. After a certain dwell time, saline is aspirated and $P\text{co}_2$ is measured in a conventional blood-gas analyser.[9 10]

There are various problems with the methods for this technique[8] that may lead to errors.[9–11] First, carbon dioxide may be lost from the aspirate during transport and second, most blood-gas analysers underestimate $P\text{co}_2$ measured in saline.[12–16] Finally, a major disadvantage of tonometry is its relative slowness, as complete equilibration between balloon and intraluminal $P\text{co}_2$ may require 60 min. As this is impractical for clinical purposes, correction factors have been provided to calculate steady state $P\text{co}_2$ when short dwell times are applied. Even with the use of these factors, dwell times of less than 30 min are discouraged as they are believed to yield inaccurate results.[17]

A hitherto overlooked source of error is the carbon dioxide impermeable deadspace of the catheter, which may have two consequences. First, with each measurement, saline that contains carbon dioxide is retained in the deadspace after aspiration and then flushed into the balloon at the next saline instillation, thereby increasing balloon $P\text{co}_2$ before each measurement cycle. This may lead to saline $P\text{co}_2$ overestimation, particularly at short dwell times. Second, the deadspace may serve as a sink for $P\text{co}_2$

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increase in the saline of the balloon, so that the correction factors may depend on the size and thus the deadspace volume of the catheter used. Conversely, this may help to explain the differences in correction factors between gastric- and sigmoid-type tonometers of different lengths.[17] Successful elimination of sources of error may widen the clinical applicability of manual tonometry in centres where the recently introduced, semi-continuous and automated air tonometry, a technique of proven reliability, is not available.[18 19]

Therefore, we studied *in vitro* the effect of the catheter deadspace on $P\text{CO}_2$ tonometry. $P\text{CO}_2$ was measured after various saline dwell times using a normal tonometer and an extended tonometer with an increased deadspace, both with and without rinsing the carbon dioxide containing deadspace of the tonometer before each measurement cycle.

Materials and methods

A steady state $P\text{CO}_2$ in a 3-litre, temperature-controlled (mean 37.0 (SD 0.2) °C) saline bath was achieved by bubbling carbon dioxide calibration gases (4.98% and 9.98% in nitrogen, both with an accuracy of 1%; NTG, Tilburg, The Netherlands) at a flow rate of 5 litre min^{-1}. Bath $P\text{CO}_2$ was assumed to have reached steady state when five consecutive measurements at 5-min intervals differed by less than 5%.

Bias and precision of $P\text{CO}_2$ measurements in saline with the blood-gas analyser (ABL 505, Radiometer, Copenhagen, Denmark) were derived from comparison of the measured bath $P\text{CO}_2$ at steady state with the expected bath $P\text{CO}_2$, calculated from the carbon dioxide content of the calibration gas, bath temperature and barometric pressure (Pbar), according to $P\text{CO}_2=(P\text{bar}-47)\times100\times\%$ carbon dioxide content. The measured bath $P\text{CO}_2$ at steady state underestimated the expected $P\text{CO}_2$: mean 4.5 (SD 0.2) kPa (n=32) *vs* 4.8 kPa ($P<0.0001$), and 8.8 (0.2) *vs* 9.6 kPa ($P<0.0001$), respectively. The bias of the $P\text{CO}_2$ measurements, defined as the mean percentage difference between measured and expected $P\text{CO}_2$, was thus −6.8%. Precision, the SD of bias, was 3.0%. Bias and precision were independent of bath $P\text{CO}_2$. Underestimation of $P\text{CO}_2$ measured in saline with the type of blood-gas analyser used is in agreement with the literature.[15–16] Thus all $P\text{CO}_2$ measurements in saline were multiplied by a factor of 1.07 (=100/93.2).

For our *in vitro* study we used TRIP Sigmoid tonometers (Tonometrics, Inc., Bethesda, MD, USA), as applied previously for gastric tonometry in healthy volunteers.[20] We did not compare sigmoid (length 202 cm) with gastric (length 150 cm) tonometers, which have different deadspaces, because the catheters not only differ in length but also in external diameter, at similar balloon properties. The correction factors for the increase in $P\text{CO}_2$ in the tonometer types differ, as stated by the manufacturer,[17] and this may indicate that the increase in $P\text{CO}_2$ as a function of time may be slower in the sigmoid-type tonometer, but the reason is not given. To evaluate the effect of deadspace on the increase in $P\text{CO}_2$ in the balloon saline as a function of time, we decided to use tonometers of the same type with different lengths and thus deadspace volumes, and the manufacturer kindly supplied sigmoid-type tonometers that were extended to 300 cm. All tonometers had identical stopcocks, balloons and tube material. The deadspace was assessed with a micro-syringe, after cutting the tube at balloon entry. The deadspace volume was 1.07±0.02 ml in the normal sigmoid-type tonometer (normal tonometer (NT), n=10) and 1.71±0.03 ml in the extended sigmoid-type tonometer (extended tonometer (ET), n=10). Carbon dioxide permeability of the tube was also assessed (n=6). After cutting off the balloon and stopcock, the tubes were filled with saline, sealed and placed in a saline bath with a $P\text{CO}_2$ value of 9.6 kPa for 24 h at 37°C. The tube was then opened, saline aspirated immediately and $P\text{CO}_2$ measured in a blood-gas analyser. $P\text{CO}_2$ increased by only 0.5±0.2 kPa at 24 h.

The time-dependent increase in $P\text{CO}_2$ in the balloons of the tonometers (n=6 NT, n=12 ET) at saline dwell times of 10, 20, 30, 45, 60 and 90 min was determined in two experiments for each type of tonometer. Each measurement cycle consisted of introducing 2.5 ml of saline into the tonometer balloon, a certain dwell time for (partial) equilibration, and aspiration. The first 1.1 ml aspirated in the NT and 1.7 ml in the ET was considered to represent the deadspace and was discarded. The final aspirate was introduced into the blood-gas analyser for $P\text{CO}_2$ measurements. In experiment I, the effect of carbon dioxide contamination of the deadspace saline on the time-dependent increase in $P\text{CO}_2$ in a bath of $P\text{CO}_2$ 4.8 kPa was evaluated. Before each measurement cycle, the following were performed: (1) rinsing of the tonometer with fresh saline; (2) filling of the tonometer with saline 2.5 ml and immersion in a saline bath at a $P\text{CO}_2$ of 4.8 kPa or 9.6 kPa for 30 min; (3) aspiration and disposal of saline 2.5 ml, thereby retaining the deadspace volume with an estimated $P\text{CO}_2$ of approximately 4.0 kPa and 8.0 kPa, respectively; and (4) placing the tonometer in a saline bath at a $P\text{CO}_2$ of 4.8 kPa for a measurement cycle. In experiment II, the increase in $P\text{CO}_2$ was determined in saline baths at $P\text{CO}_2$ values of 4.8 and 9.6 kPa, and all residual carbon dioxide in the deadspace saline was removed by rinsing the tonometer three times with 2.5 ml of fresh saline, before each measurement cycle.

STATISTICAL ANALYSIS

For experiment II, the increase in $P\text{CO}_2$ in the tonometer balloon, in terms of $P\text{CO}_2(\text{ss})$ (steady state $P\text{CO}_2$) and $T½$ (half-time), was assessed by non-linear regression analysis according to: $P\text{CO}_2(t)=((P\text{CO}_2(\text{ss})\times t)/(T½+t)$, where $P\text{CO}_2(t)=P\text{CO}_2$ at t (min) dwell time. Mean data were used to plot the regression curve. The characteristics of the increase in $P\text{CO}_2$ in the NT and ET were compared using Student's t test. Correction factors for calculation of $P\text{CO}_2(\text{ss})$ from $P\text{CO}_2(t)$ at each dwell time were calculated for each tonometer type. To judge the accuracy of $P\text{CO}_2(\text{ss})$, estimated using the correction factors at each dwell time in predicting bath $P\text{CO}_2$, we calculated the bias and precision for $P\text{CO}_2(\text{ss})$ for each dwell time. The bias represents the percentage difference in $P\text{CO}_2(\text{ss})$ and bath $P\text{CO}_2$ and precision is the SD

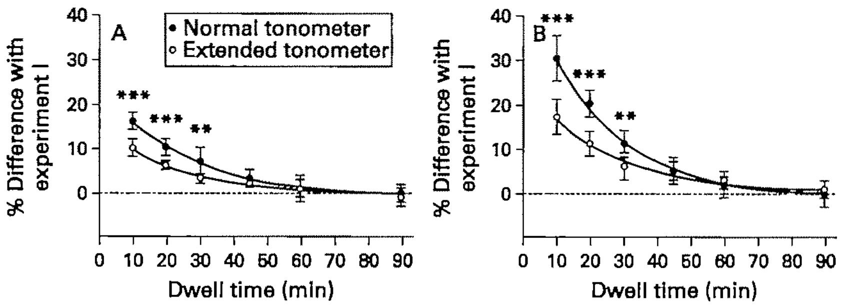

Figure 1 Effect of carbon dioxide contamination of deadspace on the increase in Pco$_2$. A: Immersion for 30 min in a bath at a Pco$_2$ value of 4.8 kPa (deadspace Pco$_2$ approximately 4.0 kPa) before each measurement cycle of Pco$_2$ increase. B: Immersion for 30 min in a bath at a Pco$_2$ value of 9.6 kPa (deadspace Pco$_2$ approximately 8.0 kPa) before each measurement cycle of Pco$_2$ increase in a bath at Pco$_2$ 4.8 kPa. Mean (SD) percentage difference in Pco$_2$ at corresponding dwell times in figure 2 and non-linear regression curve for means for the normal tonometer and extended tonometer. **$P<0.01$; ***$P<0.001$ between tonometers.

of bias. For experiment I, Pco$_2$ after each dwell time was expressed as the percentage difference in Pco$_2$ measured at corresponding dwell times in experiment II. For graphical presentation, non-linear regression curves were calculated using mean values and a one-phase exponential decay. Data are expressed as mean (SD). $P<0.05$ was considered statistically significant.

Results

EXPERIMENT I

At a deadspace Pco$_2$ of approximately 4.0 kPa (bath Pco$_2$ 4.8 kPa), the increase in Pco$_2$ was different from that in experiment II, as Pco$_2$ measured at short dwell times was increased, especially in the ET (fig. 1A). With the NT, Pco$_2$ was significantly overestimated at dwell times of 10 and 20 min by mean 10% and 6%, respectively. With the ET, Pco$_2$ overestimation after 10, 20 and 30 min was 16%, 10% and 5%, respectively. At a deadspace Pco$_2$ of approximately 8.0 kPa (bath Pco$_2$ 9.6 kPa), overestimation of Pco$_2$ at short dwell times was even greater and more pronounced with the ET (fig. 1B). In the NT, mean Pco$_2$ overestimation after 10, 20 and 30 min was 17%, 11% and 5%, respectively. In the ET, Pco$_2$ overestimation at 10, 20, 30 and 45 min was 31%, 20%, 11% and 5%, respectively.

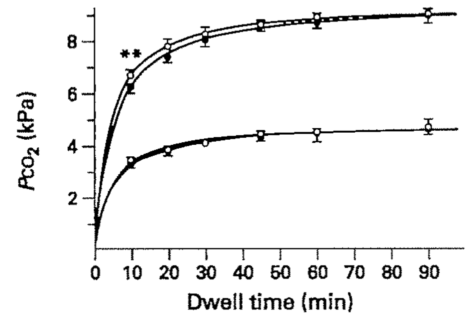

Figure 2 Increase in Pco$_2$ as a function of saline dwell time, in the normal and extended tonometer balloons in a saline bath at a Pco$_2$ value of 4.8 kPa (lower two curves) and 9.6 kPa (upper curves). Mean (SD) regression curve for means. **$P<0.01$ between tonometers.

Table 1 Mean bias and precision of Pco$_2$ tonometry for each saline dwell time, at bath Pco$_2$ values of 4.8 and 9.6 kPa. For measurement of bias and precision, the means of measurements at bath Pco$_2$ values of 4.8 and 9.6 kPa in experiment II were used. Bias is the percentage difference between bath Pco$_2$ and calculated Pco$_2$ (ss), Pco$_2$ (ss)=Pco$_2$ (t)×correction factor (t); precision is the SD of bias

Dwell time	Normal tonometer		Extended tonometer	
(t) (min)	Bias (%)	Precision (%)	Bias (%)	Precision (%)
10	−0.1	1.9	0.1	4.0
20	0.0	3.0	0.1	3.8
30	0.0	2.1	0.1	2.2
45	−0.1	2.1	0.1	2.5
60	0.0	1.5	0.1	3.0
90	0.0	3.0	0.1	2.7

EXPERIMENT II

The increase in Pco$_2$ in the tonometer balloon was described adequately by a non-linear regression model (fig. 2). The increase in Pco$_2$ in the NT was slightly faster than that in the ET, with an estimated T½ of 4.4 (0.5) and 5.3 (0.6) min, respectively ($P<0.001$). Hence, the 10-min Pco$_2$ value was significantly greater in the NT than in the ET at a bath Pco$_2$ of 9.6 kPa and the 10-min correction factors for estimation of Pco$_2$(ss) from Pco$_2$(t) differed between catheter types (1.40 (0.02) and 1.48 (0.04) for both bath Pco$_2$ values together, and for the NT and ET, respectively ($P<0.001$)). Pco$_2$(ss) in the NT and ET calculated from the non-linear regression equations did not differ from the bath Pco$_2$: Pco$_2$(ss) was 4.8 (0.1) and 4.9 (0.1) kPa at a bath Pco$_2$ of 4.8 kPa, and 9.5 (0.1) and 9.6 (0.1) kPa at a bath Pco$_2$ of 9.6 kPa for the NT and ET, respectively (ns). Bias and precision for Pco$_2$(ss) estimates, calculated from Pco$_2$(t) and correction factors for the NT and ET, were independent of saline dwell times (table 1). The pooled bias was 0.0 (0.1) % and precision was 2.7 (0.7)%, indicating accurate and reproducible Pco$_2$(ss) estimation.

Discussion

This study has indicated that a previously overlooked deadspace effect caused errors in Pco$_2$ tonometry at dwell times of less than 30 min. If this error is prevented by removal of deadspace saline containing carbon dioxide before each dwell time, $P\text{co}_2$ measurements at 10- and 20-min dwell times are as accurate as those obtained at longer dwell times, provided that correction factors are used that are specific for catheter size.

The longer T½ using the ET in experiment II, with an almost 50% larger deadspace than the NT, was probably a result of the deadspace acting as a sink for the increase in $P\text{co}_2$ in the tonometer balloon. However, the effect is only detectable at short dwell times and is probably small, as a 50% increase in deadspace reduced $P\text{co}_2$ at the 10-min dwell time by only 5%. The sink effect can be explained by diffusion of carbon dioxide into the saline of the balloon and, subsequently, into the catheter lumen and deadspace, so that the correction factors would become dependent, for a given balloon volume, on the deadspace and thereby on the length and diameter of the tonometer. With a larger sized catheter, more carbon dioxide diffuses into the deadspace and subsequently the increase in $P\text{co}_2$ in the balloon is slower. The sink effect may thus explain how measured $P\text{co}_2$, even after rinsing, is dependent on the deadspace, particularly at short dwell times and high surrounding $P\text{co}_2$ values. Indeed, the carbon dioxide diffusion rate, which depends on the pressure gradient, would be greater and therefore more dependent on the sink effect at a high surrounding $P\text{co}_2$ and a low $P\text{co}_2$ in the saline of the deadspace, that is shortly after introduction of fresh saline and start of a new measurement sequence. Conversely, reliable $P\text{co}_2$ measurements would be independent of the (size of) deadspace acting as a sink, at dwell times exceeding 10 min (fig. 2). A sink effect that depends on the ratio between catheter length and balloon volume may partly explain the difference in correction factors for gastric- and sigmoid-type tonometers provided by the manufacturer. A reduction in catheter volume to reduce the sink effect would be impracticable, as this would reduce the working length of the tonometer, and increasing balloon volume would further slow the increase in $P\text{co}_2$ in the balloon.

The most apparent effect of the tonometer deadspace on $P\text{co}_2$ measurements relates to recharging of the balloon saline by carbon dioxide-enriched deadspace saline. Failure to remove this deadspace saline before each measurement cycle resulted in overestimation of $P\text{co}_2$, particularly with the ET (experiment I) at saline dwell times of less than 30 min. This effect can be calculated, knowing the ratio of deadspace *vs* balloon volume (0.44 for the NT and 0.68 for ET), diffusion rate into the tonometer balloon and surrounding $P\text{co}_2$, using the formula: measured $P\text{co}_2$=(ratio×(deadspace $P\text{co}_2$))+(% diffusion×(surrounding $P\text{co}_2$−balloon $P\text{co}_2$)). The calculated overestimate for a 10-min dwell time, at steady state surrounding $P\text{co}_2$, would be 13% for NT and 21% for ET, which is in close agreement with our results. Similarly, it can be calculated that dwell times >30 min eliminate the effect, as equilibration is almost complete by this time. Prolonged dwell times are therefore unaffected by deadspace errors. In most clinical situations, the interval between measurement cycles can vary considerably and therefore the deadspace $P\text{co}_2$ is unpredictable, as is the way it may influence subsequent $P\text{co}_2$ determinations. There are two practicable options to eliminate the deadspace effect. Dwell times >30 min are chosen or the tonometer is rinsed before each measurement cycle. The results of experiment II (table 1) indicate that even dwell times of 10 min result in an estimation of surrounding $P\text{co}_2$ with similar bias and precision to those obtained after longer dwell times if the tonometer is rinsed before each measurement cycle. This may widen the clinical applicability of manual tonometry by allowing short-term evaluation of therapeutic interventions.

In summary, our study indicated that saline dwell times of less than 30 min yielded reliable results during $P\text{co}_2$ tonometry provided that the tonometer was rinsed before each measurement cycle and correction factors were used that were specific for catheter size. Failure to recognize the deadspace as a source of error may have affected results in recent studies on the value of splanchnic tonometry.[6–8]

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Bispectral index: comparison of two montages

J. D. Hall and G. G. Lockwood

Summary

We have compared fronto-central and bifrontal montages using a new EEG monitor, the Aspect A-1000. The monitor uses bispectral analysis to derive an index of anaesthetic depth, the bispectral index (BIS). We compared reliability, impedance and BIS for each montage. ECG electrodes placed in a bifrontal montage were more reliable than silver dome electrodes in a fronto-central montage and both types of electrodes had impedances in the clinically useful range. However, BIS values derived from each montage were found to differ in an unpredictable manner. The bifrontal montage is easy to apply and reliable but it is not comparable with a fronto-central montage. We conclude that the BIS may be useful for following trends in anaesthetic depth in individual cases but it is less helpful when making comparison between patients or as a single value. (*Br. J. Anaesth.* 1998; **80**: 342–344)

Keywords: monitoring, electroencephalography; anaesthesia, depth; equipment, EEG monitor

A non-invasive, simple to use measurement of anaesthetic depth would be of great value. The measurement should preferably be based on changes at the anaesthetic site of action, ideally would be independent of anaesthetic type, and be able to predict awareness and recovery from anaesthesia. Many attempts have been made to use electroencephalograph (EEG) derivatives such as spectral edge frequency (SEF) and power spectral analysis (PSA) to measure changes in depth of anaesthesia. A limitation of these methods is that they do not use all of the information available within the EEG signal. For example, PSA can only quantify power distribution as a function of frequency, ignoring phase information.[1] SEF and PSA are not universally successful measures of anaesthetic depth and neither are used routinely in the clinical setting.

More recently, the Aspect A-1000, a four-channel EEG monitor, has been introduced into clinical practice in an attempt to fulfil this role. It generates a single number, termed the bispectral index (BIS), which is a guide to the level of consciousness. Initial studies used a fronto-parietal[2] or fronto-central[3] montage (lead arrangements) which requires electrodes to be sited within the hairline. Such montages may be difficult to use in routine clinical practice and the supposedly more convenient bifrontal montage, with electrodes positioned on the skin of the forehead, has also been used.[4] We have compared the BIS generated from two montages to determine if it is montage-dependent. We have also compared the reliability and impedance of ECG electrodes (which may be used conveniently for the bifrontal montage) with silver dome electrodes which are needed for the fronto-central montage.

Patients and methods

After obtaining approval from the local Research Ethics Committee, we studied 15 patients undergoing routine anaesthesia and surgery. Electrodes were placed at Fp1, Fpz, Fp2, C3, C4 and mastoid. The bifrontal and mastoid electrode sites were degreased with isopropanol, abraded with Nuprep (DO Weaver and Co., USA) and paediatric silver–silver chloride self-adhesive ECG electrodes (NiKo Medical Products) applied. The scalp was abraded with Nuprep at C3 and C4 and silver dome electrodes applied using Ten 20 (DO Weaver) adhesive paste. BIS was computed by an Aspect A-1000 (software v2.51 Aspect Medical Systems, Framingham, MA, USA) from the Fp1–Fpz and Fp2–Fpz pairs and from Fp1–C3 and Fp2–C4 pairs simultaneously, using the mastoid as ground.

Data were collected by computer every 15 s from 15 patients undergoing a variety of surgical procedures. Anaesthesia was not standardized and was controlled without regard to the results produced by the EEG. Electrode impedances were recorded whenever an impedance check was requested during the case, commonly when resiting an electrode. The last impedance value only from such an episode was used in the analysis. The security of lead placement was investigated by comparing the number of cases in which the frontal ECG leads were secure throughout, to the number of cases in which the central silver dome leads were secure throughout, using Fisher's exact test. The impedances of the two electrode types were compared using the Mann–Whitney test. BIS values from the bifrontal montage and fronto-central montage were compared using scatter plots for each individual. Data from all patients were pooled and the two montages correlated. Data were processed using Excel v7.0 and Arcus Biomedical v6.8.

Results

A total of 30 h of data were collected. At least one frontal electrode needed resiting during four cases, and at least one central electrode needed resiting

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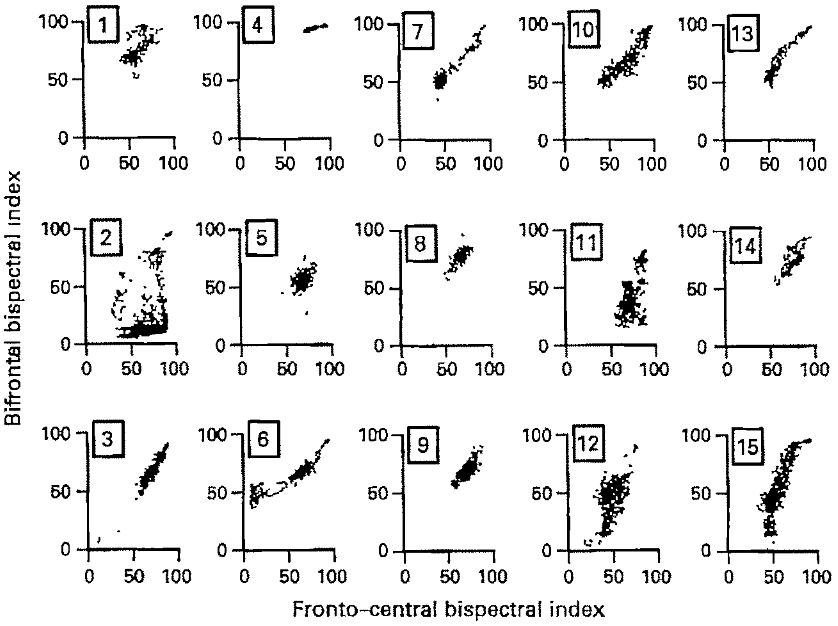

Figure 1 Fronto-central bispectral index plotted against bifrontal bispectral index for 15 patients during routine anaesthesia. Drugs administered included: methohexital (patient Nos 1, 3, 4, 5, 8, 9, 10, 12, 13 and 15), midazolam (patient Nos 2, 11, 12 and 15), fentanyl (patient Nos 2, 3, 5, 6, 7, 9, 10, 11, 12, 13, 14 and 15), morphine (patient Nos 3, 4, 6 and 8), pethidine (patient No. 1), halothane (patient Nos 2, 5 and 13), isoflurane (patient Nos 3, 4, 8, 9, 10 and 12), sevoflurane (patient Nos 1, 4 and 7), enflurane (patient Nos 6, 7 and 14), desflurane (patient No. 6) and propofol (patient Nos 1, 6, 11 and 14). The variable relationship between bispectral index derived from the two montages does not seem to be drug related, and in many individuals the difference in simultaneous bispectral index measurements is greater than the separation found between patients who moved in response to surgical stimulation and those who did not.

during 11 cases ($P < 0.02$). Median impedances were 2425 Ω (ECG electrodes) and 2700 Ω (dome electrodes). There was no difference in their distributions and values were within the clinically useful range.

Inspection of individual scatter plots of BIS from the two montages did not support the hypothesis that they were equivalent (see fig. 1). The agreement could not be improved by excluding BIS data pairs recorded during periods of poor signal quality or low total power. The pooled data revealed that the bifrontal BIS was, on average, 13 less than the fronto-central BIS and could be estimated as 0.68 (95% confidence intervals 0.65–0.71) of the fronto-central BIS.

Discussion

The EEG is a complex signal that can, through Fourier analysis, be broken down into several component frequencies. The analysis generates information on the frequency, power and phase of the signal and so facilitates interpretation. In order to use as much of the EEG signal as possible, a technique called bispectral analysis has been applied in the Aspect A-1000. This technique was developed in the 1960s by geophysicists to study retrospectively complex seismic waveforms.[5] The bispectrum is a measure of the level of phase coupling between different frequencies of the Fourier spectrum of a signal but it is difficult to interpret. Important information relating to anaesthetic effect may be contained within the phase relationships. Features of the EEG bispectrum which predicted response to surgical stimulus were defined using a stepwise regression.[6] These features were then combined using discriminant analysis into a multivariate index, with values from 0 to 100. This index is being refined and updated continually, although the details are not published, and it is known as the bispectral index (BIS). In summary, BIS is a number derived by the Aspect A-1000 from the bispectrum and other features of the EEG.

BIS has been investigated as an indicator of anaesthetic depth. One study showed that during thiopental–isoflurane anaesthesia with a fronto-parietal montage, BIS was significantly different between movers and non-movers.[6] In another study of isoflurane–alfentanil and propofol–alfentanil anaesthesia, BIS was significantly different between movers and non-movers in each anaesthetic group but could not differentiate between movers in the propofol group and non-movers in the isoflurane group.[7] BIS was also a better predictor of movement than end-expired isoflurane concentration.[7] These results suggest that BIS is dependent on the drug used in addition to depth of anaesthesia.

Regardless of its capability as a monitor of anaesthetic depth, we believe that it must be convenient to use if it is to become accepted clinically. We have not found the manufacturer's recommended electrodes (Zip-Prep, Aspect Medical Systems) to be useful within the hairline and in such positions we have had consistent success only with silver dome electrodes. Frontal electrodes are easier to apply and we have shown that they give a more reliable signal, which probably explains their adoption in more recent studies. It would be convenient if the BIS was independent of the choice of montage, but Kochs and co-workers found that EEG changes were dominant in frontal areas during isoflurane anaesthesia[8] and therefore it might be expected that different montages would give more or less sensitive indices of depth of anaesthesia.

Individual BIS data (fig. 1) showed differences between montages. Although a few cases showed excellent agreement between the two montages, in the majority the difference between the bifrontal and fronto-central BIS was too great and too unpredictable to enable them to be used interchangeably under clinical conditions. For example, when the fronto-central BIS is in the clinically important range of 60–70, 50% of bifrontal BIS measurements were outside the range 44–67 and 10% outside the range 11–77. We conclude that if comparisons between bispectral indices are to be made, it is important that the montages and anaesthetics used are the same. If bifrontal ECG electrodes are used to obtain a BIS value during anaesthesia, it is important not to act on the measured value on the basis of studies using fronto-central montages. The BIS may be useful for trends in individuals, but single values or comparison between patients are of little use.

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Laryngoscopy and fibreoptic intubation in acromegalic patients

P. HAKALA, T. RANDELL AND H. VALLI

Summary

Acromegaly is recognized as a cause of difficulty in airway management and tracheal intubation. We evaluated prospectively the conditions for laryngoscopy and fibreoptic intubation in 15 acromegalic patients. Each patient served as his or her own control. Ventilation of the lungs with a face mask was successful in all patients. In five of 15 patients the vocal cords could not be seen using the Macintosh laryngoscope with a size 5 blade. Difficult laryngoscopy was associated significantly with the number of attempts required to see the vocal cords with the fibrescope ($P<0.01$, Spearman rank correlation). The larynx could not be seen with both techniques in one patient, and the trachea was intubated blindly with the help of an introducer. Our results showed that fibreoptic intubation may prove difficult or fail in acromegalic patients. Difficulties in seeing the vocal cords with a fibrescope were present most often in patients who also had probable intubation difficulties with a rigid laryngoscope. (*Br. J. Anaesth.* 1998; **80**: 345–347)

Keywords: complications, acromegaly; larynx, laryngoscopy fibreoptic; intubation tracheal

Acromegaly is a rare clinical syndrome caused by overproduction of growth hormone. The incidence of acromegaly has been estimated to be 3–4 patients per million.[1] In the anaesthesia literature the disorder is recognized as one cause of difficulty in airway management and tracheal intubation.[2 3] The anatomical changes that may result in a difficult or failed intubation include prognathism, macroglossia, thickening of the pharyngeal and laryngeal soft tissues and the vocal cords, fixation of the vocal cords, palsy of the recurrent laryngeal nerve, decrease of the width of the cricoid arch and hypertrophy of the arytenoepiglottic and ventricular folds.[3] However, difficulties encountered in tracheal intubation in patients with acromegaly are not well documented; only case reports in such patients have been published.[4–6] According to Ovassapian, Doka and Romsa, fibreoptic intubation can be used to avoid unnecessary tracheostomy in patients with acromegaly.[7]

In this prospective study we have evaluated orotracheal intubation conditions with a laryngoscope and a fibrescope under general anaesthesia and neuromuscular block in acromegalic patients. The patients served as their own controls.

Patients and methods

The study was approved by the Ethics Committee of the Neurosurgical Clinic at Helsinki University Central Hospital. Informed consent was obtained from all patients. Over a 3-yr period, we studied all patients presenting for surgery as a result of acromegaly. The clinical diagnosis was confirmed at the Department of Internal Medicine.

Patients were premedicated with diazepam 10–20 mg orally approximately 1 h before the start of anaesthesia. One patient received no premedication because of sleep apnoea syndrome. In the operating room ECG and haemoglobin oxygen saturation (pulse oximetry) were monitored continuously.

Glycopyrrolate 0.2 mg i.v. was administered to reduce oropharyngeal secretions. After induction of general anaesthesia with thiopental and fentanyl in doses required clinically, vecuronium, pancuronium or rocuronium was used for neuromuscular block. The patient's lungs were ventilated via a face mask. Ease of ventilation was assessed and recorded: 1=easy; 2=minor difficulties; 3=very difficult, necessitating the use of an oral airway; and 4=ventilation unsuccessful. As soon as neuromuscular block was complete (TOF), laryngoscopy was performed using a Macintosh laryngoscope with a size 5 blade. The best view achieved with or without cricoid pressure was assessed according to the grading of Cormack and Lehane[8]: 1=vocal cords visible; 2=posterior part of the vocal cords visible; 3=only the tip of the epiglottis visible; and 4=epiglottis not visible. We assumed that tracheal intubation with the Macintosh laryngoscope would have been difficult or even impossible in patients with grades 3 or 4. After laryngoscopy the patient's lungs were ventilated with a face mask.

Thereafter the large size oral Berman intubating airway (Hudson, USA) was placed into the patient's mouth. The patient's jaw was lifted upwards by an assistant nurse or physician to make a view of the larynx possible. The preformed tracheal tube (Portex, id 7 or 8) was mounted over the fibrescope (Pentax FB-15P, diameter of the insertion cord 4.9 mm) and the fibrescope was advanced via the oral airway to a depth of approximately 10–12 cm. The first view at fibrescopy was recorded: 1=vocal cords; 2=mucus membrane; 3=base of the tongue; and 4=an obscure view. The instrument was guided towards the vocal cords and into the trachea. If the fibrescope could not

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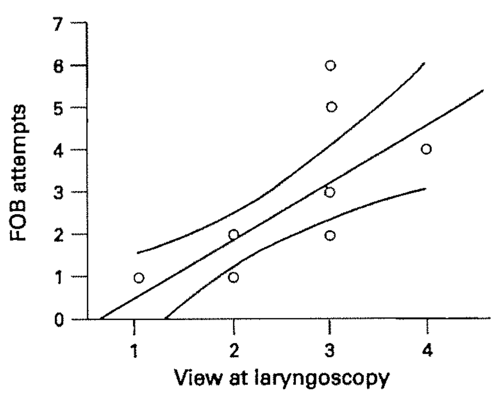

Figure 1 Correlation between the number of fibrescope (FOB) attempts required to see the vocal cords and view at laryngoscopy according to Cormack and Lehane.[8] Regression line and 95% confidence intervals are presented. Each symbol represents one or several patients.

Table 1 Description of intubations. FOB=fibreoptic bronchoscope, *n*=number of patients. * Tongue pulling method impossible because of limited mouth opening and large tongue; fourth fibreoptic intubation attempt with an Ovassapian airway. ** In one case, vocal cords could not be seen with an FOB

View of cords with laryngoscope	*n*	No. of attempts with FOB		Impingement (*n*)
		2 or fewer	3 or more	
1	4	4	0	2
2	6	6	0	4
3	4	1	3	2**
4	1	0	1*	0

be advanced into the trachea in 30 s, the procedure was interrupted for ventilation and oxygenation. A maximum of three attempts was allowed. If fibrescopy was unsuccessful, the oral airway was removed and the patient's tongue was pulled, as described by Smith, MacKenzie and Scott-Knight.[9] Jaw lift was maintained, and a 30-s fibrescopy was attempted no more than three times. The first view for each attempt was assessed as above. Times were recorded using a stopwatch by a physician or nurse.

As soon as the tip of the fibrescope was in the trachea close to the carina, the intubation tube was railroaded into the trachea. The number of fibrescope attempts was recorded. If resistance to the tracheal tube was encountered during intubation, the tube was manipulated as described in our previous study.[10] Any impingement or manipulations needed to complete tracheal intubation were recorded.

If fibreoptic intubation with the above techniques failed, the patient's trachea was intubated with the help of a rigid laryngoscope. In cases of difficult laryngoscopy, any acceptable technique to establish an airway was allowed, and a note was made. Intubations were performed by any of the authors, all being experienced with the fibreoptic technique.

For analysis of the data, the Spearman rank correlation or Fisher's exact test was used. $P<0.05$ was considered statistically significant.

Results

We studied 15 patients (nine females, six males) and every patient served as his or her own control for laryngoscopy using a size 5 Macintosh blade and a flexible fibrescope. Mean age of the subjects was 53 (range 22–68) yr. Mean weight and height were 85 (SD 19) kg and 173 (7) cm, respectively. All patients had typical manifestations of acromegaly.

Anaesthesia was induced with a mean dose of thiopental 6.3 mg kg^{-1} and fentanyl 3.7 μg kg^{-1}. Ventilation with a face mask was successful in all patients, and was easy on five occasions. An oral airway was needed in four cases. The ease of mask ventilation was not associated with subsequent intubation difficulties. The best view at laryngoscopy was graded as 1 in four patients, 2 in six (in three of whom the posterior part of the vocal cords was seen with cricoid pressure), 3 in four and 4 in one patient. When the best views at laryngoscopy were grouped as 1 and 2 denoting those in whom intubation with the aid of a Macintosh blade would be successful, and 3 and 4 as those in whom intubation would be difficult or fail, the vocal cords could be seen with the fibrescope in all but one of the latter group. The grade was associated significantly ($P<0.05$) with the number of attempts required to see the vocal cords with the fibrescope (fig. 1). None of the patients with view 1 at laryngoscopy required more than one fibrescope attempt. The first fibrescope attempt was successful in six of nine females and in three of six male patients (ns).

The frequency of resistance to the tracheal tube was eight of 15 patients (five females and three males) (ns). Manipulations led to oesophageal intubation in one instance but subsequent intubation with the help of the fibrescope was successful. On one occasion the manipulations did not lead to tracheal intubation and the patient's trachea was intubated with the help of a laryngoscope. One fibrescope attempt failed and the trachea was intubated blindly with a laryngoscope and introducer. A summary of the views at laryngoscopy, number of fibrescope attempts and impingements are presented in table 1.

None of the patients became desaturated (oxygen saturation <90%) during the study. After surgery the trachea was extubated successfully in the operating room without respiratory distress.

Discussion

Our results showed that fibreoptic intubation may prove difficult or fail in acromegalic patients. Even more important, difficulty in seeing the vocal cords with the fibrescope were encountered in patients with a grade 2–4 view at rigid laryngoscopy. In general, the causes of problems in advancing the fibrescope towards the larynx and to the trachea are blood and secretions in the oropharynx, distorted anatomy of the upper airway or inexperience with the technique.[2] Furthermore, the choice of oral airway can affect the ease of seeing the vocal cords.[11] In our study, in one case an Ovassapian airway was needed to complete fibrescopy. The tongue pulling method as an alternative to an oral airway has been used successfully by Smith, MacKenzie and Scott-Knight.[9] We found tongue pulling an acceptable option on two occasions, but in one patient with limited mouth opening, the tongue was too large to allow free advancement of the fibrescope to the oropharynx and further to the trachea.

Difficulties in seeing the vocal cords (i.e. best view graded 3 or 4[8]) with the conventional Macintosh laryngoscope were encountered in five of the 15 acromegalic patients. A grade different from that presented by Cormack and Lehane was used to assess the view at fibrescopy for several reasons: the first fibreoptic view is affected by the type of fibrescope, the model of the intubating airway (if it is used), force of jaw thrust and depth of advancement of the fibrescope. There are no reports on the incidence of difficult airway in acromegalic patients. Our findings suggest that intubation difficulties may occur more often in this group of patients than in those presenting for general surgery.[12–14] The number of patients is small because of the low incidence of the disease.[1] However, each subject served as his or her own control to assess the ease of seeing the vocal cords with each technique.

Lack of preoperative assessment of the airway can be considered a possible weakness of our report. However, the aim of the study was to evaluate the applicability of fibreoptic intubation in this group of patients, and in our opinion, the most commonly used tests for prediction of intubation difficulties do not apply to fibreoptic intubation. In fact, prediction of difficult fibreoptic intubation has not been studied, probably because the technique has been recognized as one of the best methods to manage a difficult airway.[15]

Fibreoptic intubation can prove difficult or fail, regardless of the ability to see the vocal cords.[15] In the present study the frequency of resistance to the tracheal tube was higher (eight of 15 patients) than expected from our previous results (five of 44 cases). The size of the tubes and type of fibrescopes used were similar to those in the present study.[10] We encountered impingement of the tracheal tube on eight occasions, and in seven manipulations led to successful intubation. One fibreoptic intubation failed. The causes of resistance to the tracheal tube on intubation with the fibrescope are not well elucidated. The design of the tip of the tracheal tube may explain some of the difficulties.[16] For trans-sphenoidal surgery a preformed tube is preferred, and tubes with a standard tip are the only ones available commercially. An armoured flexible tube may be an option,[17] but unpublished observations showed that intubation difficulties were not avoided by the use of such a tube (Hakala, Randell and Valli, unpublished observations). The size of the tracheal tube in relation to the outer diameter of the fibrescope has been shown to affect the rate of impingement.[10 18]

The method of choice for intubation in acromegalic patients remains unclear. Although we did not experience any case of inability to ventilate the lungs with a face mask, this risk must be taken into consideration. Similarly, in case reports of three patients, ventilation with a face mask was successful, but one difficult intubation was encountered.[4] When a difficult intubation with a Macintosh laryngoscope is anticipated, techniques other than managing the airway with a fibrescope should also be considered. Awake intubation under topical anaesthesia and sedation is the safest way to proceed if difficulties in ventilation and intubation are expected. Fibreoptic intubation in patients with acromegaly requires expertise and knowledge of alternative ways to guide the instrument towards the trachea, and manipulations of the tracheal tube are likely to lead to successful intubation on impingement.

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LABORATORY INVESTIGATIONS

Effect of continuous spinal remifentanil infusion on behaviour and spinal glutamate release evoked by subcutaneous formalin in the rat

H. BUERKLE, M. MARSALA AND T. L. YAKSH

Summary

Injection of formalin into the hind paw of the rat evokes a biphasic nociceptive behavioural response, which is considered to be an animal model of postoperative pain in humans. The initial response (phase 1) is caused by activation of peripheral nociceptors and is followed by a second phase attributed to ongoing activity in primary afferents and increased sensitivity of dorsal horn neurones. The latter effect is thought to result from glutamate-mediated *N*-methyl-D-aspartate receptor activation. In studies to date it has been difficult to discriminate mechanisms underlying phase 1 and phase 2 events because of the long-lasting half-times of intrathecally administered opioids. To further understanding of the opioid pharmacology of the two different phases of the formalin test, we have studied behavioural activity and spinal glutamate release after intrathecal administration of remifentanil, a new short-lasting μ opioid. Intrathecal remifentanil 3 μg μl^{-1} min^{-1} delivered during phase 1 inhibited behavioural response during phase 1 (100%), but did not abolish subsequent phase 2 behavioural activity completely (67 (12) %). Intrathecal remifentanil administered separately in phase 1 and phase 2 revealed a similar ED$_{50}$ (0.2 μg μl^{-1} min^{-1}) for inhibition of the behavioural responses. *In vivo*, spinal microdialysis showed incomplete reduction in glutamate concentrations in response to intrathecal remifentanil administration; this in turn inhibited phase 1 behavioural responses. Therefore we contend that supramaximal doses of intrathecal remifentanil sufficient to inhibit phase 1 activity still permitted sufficient glutamate release to allow spinal facilitation. Incomplete suppression of spinal excitatory neurotransmitter release by intrathecal opioids is consistent with spinal wind-up that is triggered during phase 1 and results in phase 2 afferent drive. This might reflect one of the mechanisms underlying postoperative pain. (*Br. J. Anaesth.* 1998; **80**: 348–353)

Keywords: pain, experimental; analgesics opioid, remifentanil; rat

The formalin test as a preclinical model of tonic persistent inflammatory pain is a well established model of postoperative inflammatory pain licking.[1-3] Subcutaneous injection of formalin into the paw evokes a biphasic behavioural response: phase 1 starts immediately after formalin injection and is characterized by paw flinching and licking. After a short period of quiescence this is followed by a second phase of paw flinching and licking.[1,2,4,5] Intrathecal delivery of *N*-methyl-D-aspartate (NMDA) receptor antagonists before injection of formalin, but not between phases 1 and 2, diminished markedly phase 2. This observation has led to the suggestion that phase 2 depends on the acute release of the excitatory neurotransmitter glutamate from neurones during the initial afferent barrage.[6-12] Indeed, in previous work by Malmberg and Yaksh in conscious rats using an intrathecal loop dialysis system, it was demonstrated that glutamate concentrations increased acutely during phase 1, but not during phase 2.[6] In this study intrathecal morphine delivered before phase 1 reduced behavioural response in phase 1 and continued to suppress phase 2 behaviour even though opioid receptor antagonism was accomplished between phase 1 and phase 2.[6] A major limitation of this study was the use of naloxone to confine opioid activity to the time period of phase 1. Thus, interfering interactions with other endogenous transmitter systems in inflammatory pain mechanisms would also be lost.

In a previous study we were able to demonstrate rapid onset of analgesia by intrathecal administration of the new short-lasting μ opioid, remifentanil, within 12 min after the start of a continuous infusion followed by a concomitant fast rate of recovery within 7 min after termination of the infusion.[15] Therefore, a more precise test to examine transient activation of the spinal opioid receptor can be achieved using this new μ opioid which, because of its rapid metabolism, allows opioid activity to be confined to phase 1 of the formalin test.[14,15] Moreover, we speculate that doses of intrathecal remifentanil that suppress behavioural responses in phase 1 should result in concurrent inhibition of glutamate release.

Materials and methods

The study was approved by the Institutional Animal Care Committee of the University of California, San Diego. Rats (male Sprague–Dawley, Harlan Indus-

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tries, Indianapolis, IN, USA; 300–350 g) were implanted with intrathecal catheters and thereafter kept in separate cages on a 12-h light–dark cycle and given water and food *ad libitum.* Each rat was implanted as described below with an intrathecal catheter or microdialysis system, or both. Animals were allocated randomly to treatment groups and were used only once. The animals were killed after the experiment was completed.

ANIMAL PREPARATION

Before surgery animals were anaesthetized with 2–3% halothane and 50% oxygen in air, breathing spontaneously via a mask. Surgical insertion of the intrathecal catheters was performed using a modified version of techniques described previously.[16] Intrathecal catheters were made of polyethylene tubing (PE-10, id 0.28 mm, od 0.61 mm) tied at one end into a small knot for fixation under the skin. After shaving and preliminary cleaning of the surgical area with alcohol and betadine, the rat was placed in a stereotaxic apparatus. After incision of the atlanto-occipital membrane, the intrathecal catheter was inserted into the intrathecal space and passed to the rostral edge of the lumbar enlargement, 8.5 cm posterior to the cisterna magna. The external arm of the catheter was then tunnelled subcutaneously and fixed under a skin suture. Only animals with normal motor functions were used in the experiments.

BEHAVIOURAL TESTING: FORMALIN TEST

For behavioural testing conscious rats were connected to different intrathecal catheters (see below) and placed in round Plexiglass cages (9 × 35 cm) on top of a temperature-maintained glass surface (30 °C). A mirror was set up to improve visibility of the animal's behavioural responses. An adaptation period of 15 min was allowed, and then each animal was picked up gently by another investigator and 50 µl of 5% formalin were injected s.c. into the right hind paw. The animal was replaced in its cage. Flinches of the right hind paw without concomitant movement of the left hind paw or stepping motion were counted as behavioural response and were evaluated at 1–2, 5–6, 9–10 and 14–15 min, and continued at 5-min intervals up to 60 min after injection of formalin. The interval from 0–10 min was defined as phase 1 of the formalin test (acute C-fibre stimulation) and the interval from 10–60 min was defined as phase 2.

CONSTRUCTION OF MICRODIALYSIS CATHETER

Intrathecal loop dialysis catheters were constructed from hollow fibres (200 µm id, 300 µm od, 11 kDa molecular weight cut-off; Filtral, AN 69-HF). An 18-cm length of fibre was coated with a thin layer of epoxy (Devcon Corp., Danvers, MA, USA) except for a 4-cm portion in the middle. Nichrome-Formvar wire (0.0026 mm; A-M systems, INC., Everret, WA, USA) was passed through the fibre and both ends of the fibre were attached to pieces of silicon PE-10 (3.5 cm length) with cyanoacrylate (Borden, Inc., Columbus, OH, USA). The fibre was then bent such that the uncoated portion formed a "U"-shaped loop. Finally, both pieces of silicon PE-10 were bound together with silicon rubber at the level of their junction with the dialysis fibre.[17 18]

IMPLANTATION OF THE CATHETER

To implant the microdialysis catheter, a technique similar to that described for placement of intrathecal catheters was used.[17 18] After the surgical procedures, a recovery period of 5 days was allowed before initiating sampling and testing of dialysate. The neurological status of the animal was assessed after surgery and before dialysate testing; neurological status was evaluated after flushing the intrathecal catheter with 10 µl of normal saline. Animals with impaired motor function were killed.

PERFUSION OF CATHETERS

To initiate dialysis, one of the externalized silicon PE-10 connections was attached to a 50-cm length of PE-10 tubing (inflow) and the other arm to a 50-cm length of PE-10 (outflow). A syringe pump (Harvard Compact Infusion Pump, Model 975, MA, USA) fitted with a 5-cc plastic syringe was used to perfuse the dialysis tubing with artificial cerebrospinal fluid (ACSF) at a rate of 10 µl min^{-1}. ACSF contained (nmol litre^{-1}): Na^+ 151.1, K^+ 2.6, Mg^{2+} 0.9, Ca^{2+} 1.3, Cl^- 122.7, HCO$_3$ 21.0, HPO$_4$ 2.5 and glucose 3.5. ACSF was bubbled with 95% oxygen–5% carbon dioxide before each experiment to adjust the final pH to 7.2. All experimental manipulations were preceded by a 30-min washout period and collection of two control samples (10 min each).[17]

SAMPLE COLLECTION AND ANALYSIS

Dialysate samples were collected on ice and kept frozen at −20 °C until analysed for amino acids. All dialysis samples were analysed routinely for glutamate content using the PITC (phenyl isothiocyanate) derivatization procedure and a Waters HPLC with a reverse phase C18 column (3.9 × 300 mm, 4-µm particle) and UV detector. Amino acid content was measured in single 25-µl aliquots of dialysate. Methionine sulphone was added to each dialysate sample as an internal standard. Sensitivity was 5–10 pmol/injection. Amino acid peak heights were normalized initially to the methionine sulphone peak and then quantified based on a linear relationship between peak height and amounts of corresponding standards. External standards were run daily.

FORMALIN TEST AND INTRATHECAL PERFUSION IN AWAKE ANIMALS

Formalin was injected s.c. into the hind paw after the microdialysis system was perfused for 30 min (washout period) and two baseline samples (10-min duration each) were collected. After injection, samples were collected at 10-min intervals until 20 min after injection and then at 20-min intervals after injection (samples until 10 min=phase 1, samples from 10 to 60 min=phase 2).

DRUGS

Drugs given intrathecally in this study were remifentanil HCl (molecular weight=369) (Glaxo, Research

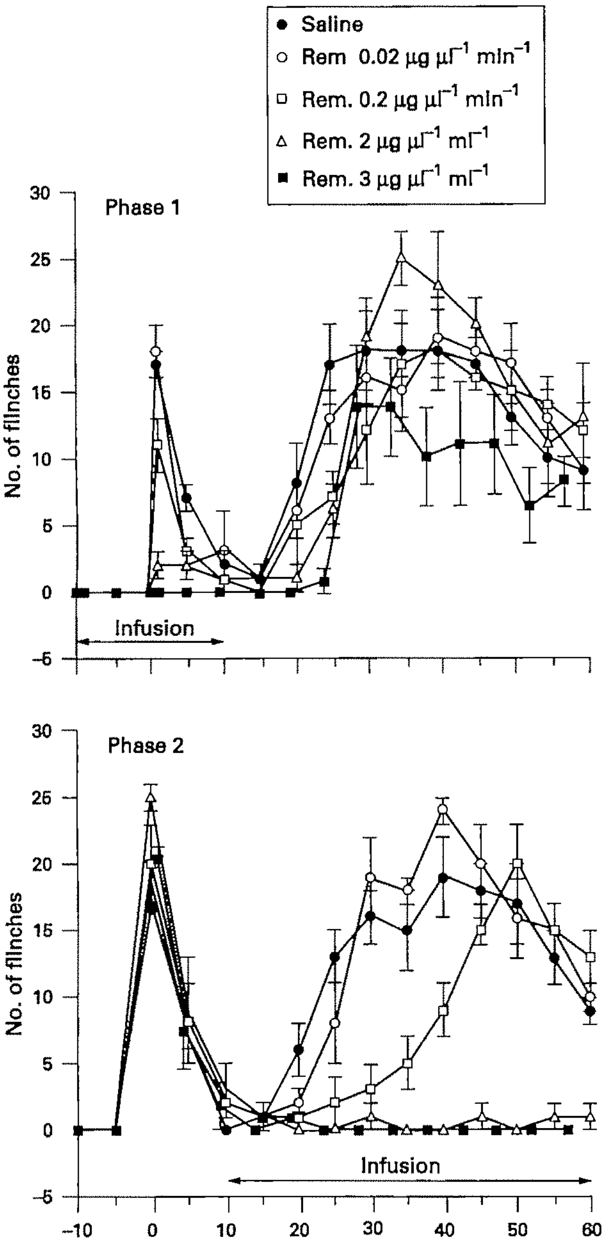

Figure 1 Time–effect curves for intrathecal infusion of remifentanil (Rem.) during phases 1 and 2 of the formalin test. The behavioural time–effect curves with intrathecal administration of remifentanil during phases 1 (−10 until +10 min) (top) and 2 (from 10 until 60 min after formalin injection) (bottom) of the formalin test are shown. The number of flinches per minute after injection of 5% formalin 50 μl s.c. in the hind paw are given. Formalin injection was performed at 0 min. Data are mean (SEM) of 5–8 animals.

Triangle Park, NC, USA) and normal saline as control. Intrathecal remifentanil infusion rates are expressed in μg μl^{-1} min^{-1}. Intrathecal injection was achieved by connecting the animal to a microinjection syringe pump (Harvard Instruments) before testing via a length of calibrated PE-50 tubing. Intrathecal drug was injected at a flow rate of 1.0 μl min^{-1}. Thus the lowest total amount of intrathecal remifentanil was 0.4 μg for the phase 1 infusion of 0.02 μg μl^{-1} min^{-1}; the highest amount for phase 1 (3 μg μl^{-1} min^{-1}) was remifentanil 60 μg.

In a separate experiment, animals receiving a supramaximal dose of intrathecal remifentanil for phase 1 suppression were given naloxone (Dupont Pharmaceutical, Wilembur, USA) 0.5 mg/kg body weight i.p., 10 min after injection of formalin. This experiment served as a control for residual intrathecal remifentanil activity affecting phase 2. All drugs were dissolved in sterile normal saline.

STATISTICAL ANALYSIS

Behavioural data are expressed as mean (SEM) number of flinches per minute for 1, 5, 10, 15 min, and at 5-min intervals up to 60 min. Statistical analysis of the behavioural data was performed using the one-way ANOVA test followed by the Student's Newman–Keuls multiple comparisons test. For illustration, the dialysate group was calculated as percentage change in baseline values (mean (SEM)). Statistical analysis of glutamate release was performed by the Kruskal–Wallace test. For all statistics, $P<0.05$ was considered significant. Dose–response curves are presented as percentage of the maximal possible effect (%MPE). For all drugs, the dose–response analysis, as described by Tallarida and Murray, was performed.[19] ED$_{50}$ and 95% confidence intervals were calculated using the least squares linear regression model, where the log dose values were used.[19]

Results

INTRATHECAL INFUSION OF REMIFENTANIL BEFORE AND DURING PHASE 1

Injection of formalin resulted in a biphasic incidence of flinching of the formalin injected paw, as demonstrated in the animals receiving intrathecal saline infusion during phases 1 and 2 (fig. 1). Intrathecal infusion of remifentanil during phase 1 and intrathecal saline during phase 2 resulted in complete dose-dependent suppression of phase 1 behaviour ($P<0.05$ compared with saline controls).

Intrathecal remifentanil at the highest dose (3 μg μl^{-1} min^{-1}) during phase 1 resulted in an approximate 40% reduction in the magnitude of phase 2 behaviour compared with the control groups (fig. 2) ($P<0.05$). To emphasize that depression of phase 2 did not result from residual action of remifentanil during phase 2, studies with phase 1 intrathecal remifentanil infusions were repeated with administration of naloxone 0.5 mg kg^{-1} i.p., 10 min after injection of formalin. Phase 2 suppression was unaltered, emphasizing that the persistent effects were not caused by residual opioid agonist action during the second phase (see fig. 2).

INTRATHECAL INFUSION OF REMIFENTANIL DURING PHASE 2

Intrathecal infusion of saline in phase 1 and intrathecal infusion of remifentanil during phase 2 revealed no difference in phase 1 behaviour compared with control animals ($P>0.05$), whereas remifentanil blocked phase 2 of the formalin test in a dose-dependent manner (intrathecal remifentanil 0.2, 2.0 and 3 μg μl^{-1} min^{-1}; $P<0.05$) (see fig. 1). The ED$_{50}$ for remifentanil was similar for suppression of both phases (phases 1 and 2: 0.2 μg μl^{-1} min^{-1} (95% CI 0.1–0.4 μg μl^{-1} min^{-1})) (fig. 3).

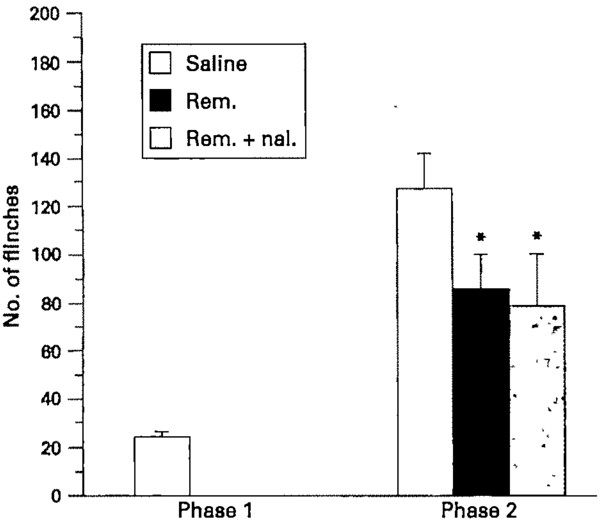

Figure 2 Behavioural activity in phase 2 after intrathecal administration of remifentanil $3\ \mu g\ \mu l^{-1}\ min^{-1}$ in phase 1 followed by naloxone i.p. Behavioural activity is expressed as number of flinches during phases 1 and 2 after phase 1 intrathecal continuous delivery of saline, remifentanil (Rem.) alone or remifentanil $3\ \mu g\ \mu l^{-1}\ min^{-1}$ followed by naloxone (nal.) i.p. As indicated for intrathecal remifentanil, no behavioural activity was observed during phase 1 and no difference was seen in phase 2 activity for animals treated with naloxone. Data are mean (SEM) of 5–8 animals. *Significant reduction in phase 1 behaviour in animals given intrathecal remifentanil compared with control animals ($P<0.05$).

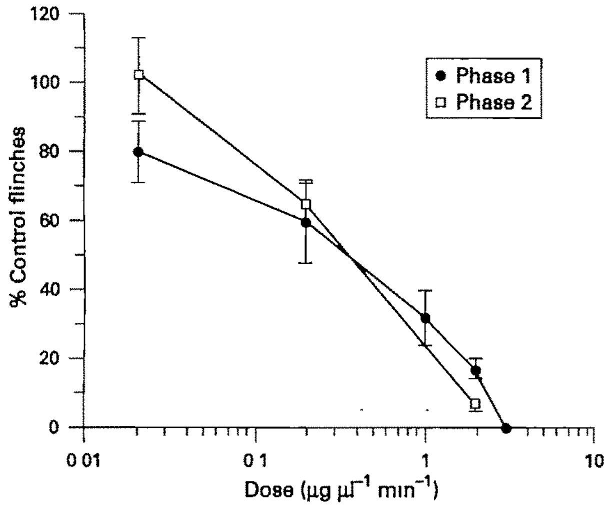

Figure 3 Dose–response curves of intrathecal remifentanil for inhibition of phase 1 and phase 2 behavioural activity. The dose–response curves for intrathecal delivery of remifentanil in phases 1 and 2 to suppress behavioural activity in each phase are shown. Data are mean (SEM) of 5–8 animals.

SPINAL GLUTAMATE RELEASE

Before treatment, measurable glutamate concentrations were present in the spinal dialysate of the unanaesthetized rat with stable baselines for saline control and intrathecal remifentanil groups. Formalin injection resulted in an increase in glutamate concentrations, which was consistently evident during the first 10 min after formalin injection in the intrathecal saline compared with the intrathecal remifentanil group (71 (34) % *vs* 21 (36) %; $P<0.05$). This release corresponded to the appearance of phase 1 behaviour. After phase 1, glutamate concentrations decreased and reached baseline values during phase 2 in both groups (fig. 4).

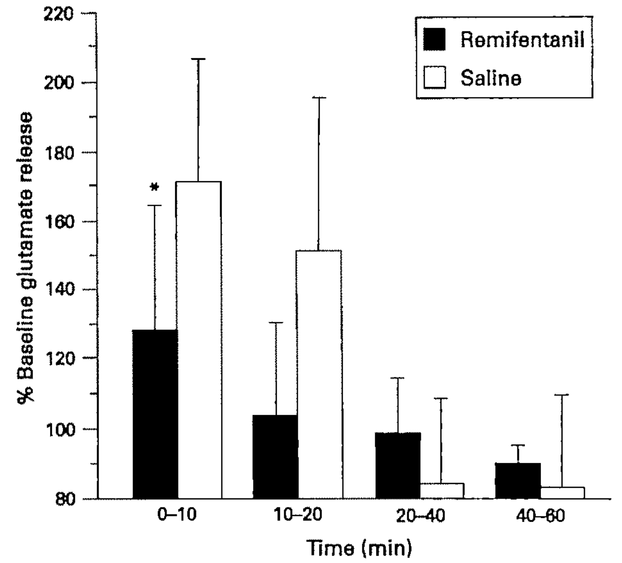

Figure 4 Intrathecal remifentanil during phase 1 and glutamate release during both phases of the formalin test. Release of glutamate in phases 1 and 2 after intrathecal administration of remifentanil $3\ \mu g\ \mu l^{-1}\ min^{-1}$ or intrathecal saline $1\ \mu l\ min^{-1}$ during phase 1 is shown. Glutamate concentrations were assessed by *in vivo* spinal microdialysis and calculated as change in percentage over baseline concentrations for intrathecal administration of saline or remifentanil. *Significant reduction in glutamate release for the intrathecal remifentanil group ($P<0.05$). Data are mean (SEM) of eight animals.

Discussion

The formalin test has been used widely as a model of inflammatory pain[1 2] to investigate the mechanisms and pharmacology of spinal facilitation. Assessment of peripheral afferent activity has emphasized that injection of the irritant formalin leads to an acute barrage of small primary afferents followed by low level, but persistent, afferent activity. The corresponding activity in dorsal horn neurones[21] and behaviour sequelae suggests a second phase of behaviour that is unexpectedly prominent given the magnitude of the afferent input during this second phase. The ability to reduce (but not completely block) this second phase by spinal delivery of NMDA receptor antagonists given before formalin injection is believed to reflect the role of glutamate release during this acute interval in triggering the second phase facilitation.[22] It was suggested that block of afferent activity by opioids during the first phase should diminish the second phase behavioural response.[23] In previous work, we used intrathecal morphine and blocked the opioid receptor during the second phase by delivery of naloxone between phases 1 and 2.[24] However, interpretation of these results was hindered by rebound hyperalgesia that can occur after using the antagonist naloxone.[25]

Therefore, in our study we were able to address this hypothesis more accurately by the use of the short-lasting opioid agonist remifentanil. This lipid soluble agent is cleared rapidly from the intrathecal space and metabolized in plasma by plasma esterases.[15 26] As we have shown previously in the rat model, continuous infusion of remifentanil rapidly achieves steady state levels within approximately 5–10 min and shows also a concomitantly fast rate of recovery after termination of remifentanil delivery.[15] Thus remifentanil appears to be useful in this model of inflammatory pain .[25 27] Further confirmation of the lack of a persistent opioid receptor occupancy by intrathecal remifentanil was obtained in our study by giving naloxone after phase 1, and the observation that naloxone had no effect on phase 2 activity. As shown previously for systemic administration of remifentanil,[27] intrathecal doses of remifentanil abolishing phase 1 behavioural activity completely did not result in complete reduction of phase 2 responses. Further increasing doses of intrathecal remifentanil during phase 1 in our study were limited by respiratory complications. Thus we suspect that the observed suppression in this model reflects the maximum achievable effect by intrathecal remifentanil. The present behavioural part of this study suggests that suppression of behaviour is not an indicator of changes during a phase 2 state of facilitatory spinal transmission.

SPINAL MICRODIALYSIS AND GLUTAMATE RELEASE

Glutamate has been shown to be the major excitatory amino acid neurotransmitter in the central nervous system, playing a key role in central sensitization and spinal pain transduction mechanisms.[28] The limitations of the dialysis model are that laminar or cellular origins of extracellular transmitters cannot be determined. In our model, glutamate concentrations have been shown to be increased in the spinal extracellular dialysate after high, but not low, intensity stimulation (Marsala and colleagues, 1995, unpublished observations). Earlier studies have shown that these increased concentrations may be suppressed by systemic morphine.[24] Accordingly, the release may derive from primary afferent or interneurones, both sources having been shown to contain this amino acid.[11 29 30]

Opioids are known to reduce small afferent transmitter release (e.g. substance P, CGRP or amino acids).[31] Thus the opioid effect observed in the present study might reflect a change in afferent glutamate secretion. On the other hand, it is believed that the NMDA receptor is postsynaptic to a non-afferent terminal.[32] Thus the opioid effect may reflect inhibition of the interneurone. Mu opioids such as remifentanil are known to induce hyperpolarization by increase in potassium conductance,[33] thereby reducing neuronal excitability. This would predictably lead to a reduction in the release of endogenous transmitters, such as glutamate, as shown during phase 1 in our study. However, even when the noxious stimulus was blocked completely, glutamate release was not abolished in the present study. This finding is in accordance with observations by Abbadie and colleagues[25] showing expression of c-*fos* in the rat spinal cord despite administration of remifentanil during phase 1 of the formalin test.

In conclusion, we have shown dose-dependent suppression of phase 1 and 2 behaviour of the formalin test after intrathecal administration of the short-lasting μ opioid remifentanil in awake animals. With regard to behavioural responses and concomitant spinal glutamate release after intrathecal remifentanil, we suggest that spinal μ opioid receptors modulate but do not abolish the mechanisms underlying spinal sensitization in this model of inflammatory pain.

Acknowledgement

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British Journal of Anaesthesia 1998; **80**: 354–359

Changes in right atrial catecholamine content in naïve rats and after naloxone-induced withdrawal

J. V. RABADÁN, M. V. MILANÉS AND M. L. LAORDEN

Summary

In this study, we determined if changes in heart catecholamine content during naloxone-induced withdrawal correlated with modifications in heart rate. In addition, we determined plasma concentrations of corticosterone as an index of the hypothalamo–pituitary–adrenal (HPA) axis. The effects of naloxone on norepinephrine, epinephrine or dopamine content and turnover, plasma concentrations of corticosterone and the mechanical response of the right atria of the rat were studied. Male rats were implanted with placebo or morphine pellets for 7 days. On the day of sacrifice, animals were injected with saline or naloxone 1 mg kg^{-1} s.c. to precipitate a withdrawal syndrome. Administration of naloxone to morphine-treated (tolerant) animals induced a decrease in atrial content of norepinephrine, epinephrine and dopamine (290.2 (11.9) ng g^{-1}, 15.6 (2.1) ng g^{-1} and 9.52 (0.5) ng g^{-1}, respectively) and an increase (1.38 (0.2) ng g^{-1} in the dihydroxy phenyl acetic acid/dopamine (DOPAC/DA) ratio. Administration of naloxone to morphine-treated animals enhanced plasma concentrations of corticosterone (435.8 (27.6) ng ml^{-1}). In the isolated right atria, L-naloxone induced an increase in atrial rate in preparations from morphine-treated rats whereas in placebo-pelleted (naïve) rats, L-naloxone induced a decrease. In contrast, administration of D-naloxone (inactive isomer) produced a decrease in atrial rate in preparations from placebo or morphine-treated rats. We conclude that this study has provided evidence that naloxone-induced withdrawal was characterized by activation of catecholaminergic neurones in the heart that was accompanied by an increase in atrial rate. (*Br. J. Anaesth.* 1998; **80**: 354–359)

Keywords: heart, heart rate; sympathetic nervous system, catecholamines; antagonists opioid, naloxone; rat

Chronic administration of opioids, particularly morphine, produces tolerance to many of their pharmacological effects. Physical dependence on opioids develops after repeated administration, as evidenced by the appearance of distressing physical symptoms after its withdrawal, but its intensity depends on the specific type of opioid agonist used.[1] In general, drugs acting primarily at μ opioid receptors, such as morphine and heroin, are highly addictive, whereas those acting at the κ site produce a mild degree of physical dependence.[2]

The mechanisms by which opioid tolerance and dependence develop are still not clearly understood.[3] Different mechanisms have been sought to explain the development of opioid tolerance–dependence and the effects on drug withdrawal, including adaptative changes in neurotransmitter systems that appear to be targets of opioids (for review see Nestler[4]). Several attempts have been made to ascertain the possible role of catecholamines in the genesis or expression of dependence processes. The noradrenergic system has been demonstrated to play an important role in opioid dependence and withdrawal,[4] and studies of opioid regulation of the noradrenergic system have focussed mainly on the locus coeruleus. Thus precipitation of withdrawal in morphine-dependent rats by administration of opioid antagonists caused an increase in firing of norepinephrine neurones in the locus coeruleus and an increase in the turnover of norepinephrine in the forebrain, in addition to a behavioural syndrome that has been associated with these effects.[5 6]

Also, it has been proposed that opioids can affect the activity of the hypothalamo–pituitary–adrenal (HPA) axis indirectly by altering noradrenergic neurotransmission[7 8] and attempts have been made to relate opioid-induced changes in hypothalamic noradrenergic activity to alterations in corticosterone secretion (as a marker of the HPA axis).[9 10] Moreover, it has been demonstrated that chronic administration of morphine increases the hypothalamic content of norepinephrine. However, during naloxone-induced withdrawal, the hypothalamic content of norepinephrine decreased and was accompanied by a parallel increase in plasma concentrations of corticosterone.[11 12] There is substantial evidence that noradrenergic neurones in the locus coeruleus and hypothalamus are involved in opioid dependence and withdrawal,[5 12] yet little data are available on the cardiovascular changes during morphine tolerance or dependence. It has been suggested that chronic administration of U-50,488H induced tolerance to cardiac function, which was not accompanied by down-regulation of κ binding sites.[13] In addition, a few studies indicated that catecholamines play an important role in the manifestation of the abstinence response in morphine-dependent rats. Thus adminis-

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tration of naloxone to tolerant rats produced an increase in plasma concentrations of catecholamines.[14,15]

As the different symptoms of withdrawal may involve the central and peripheral nervous systems, in the present study we determined the changes in the content of norepinephrine, epinephrine, dopamine and its metabolite dihydroxy phenyl acetic acid (DOPAC) in the right atria during morphine tolerance and withdrawal. In addition, we examined if such changes were correlated with alterations in atrial rate in isolated right atria of the rat. As an index of HPA activity, simultaneously with atrial content of catecholamines, we measured plasma concentrations of corticosterone.

Materials and methods

The study was approved by the local Animal Use Committee. Male Sprague–Dawley rats (200–250 g) were housed 4–5 per cage under a 12-h light–dark cycle (light 08:00–20.00) in a room with controlled temperature (22±1 °C) and humidity (50±10%), and food and water were available *ad libitum.*

EXPERIMENTAL PROCEDURE

On the basis of previous studies,[12,16,17] rats were rendered dependent on morphine by s.c. implantation of morphine base pellets (75 mg). The implantation schedule consisted of one pellet on day 0, two pellets on day 2 and three pellets on day 4.[18] Control animals received placebo pellets (lactose) according to the same schedule. A withdrawal syndrome was induced by injecting naloxone 1 mg kg^{-1} s.c. on the morning of sacrifice (day 7) to rats implanted with morphine pellets. The control group implanted with placebo pellets was also injected with naloxone. Animals were killed 30 min after injection.

There were four experimental groups: (1) chronic placebo–acute saline s.c.; (2) chronic placebo–acute naloxone s.c.; (3) chronic morphine–acute saline s.c.; and (4) chronic morphine–acute naloxone s.c.

CORTICOSTERONE ASSAYS

At the end of treatment, rats were killed by decapitation between 09:30–10:00 to avoid circadian variations in plasma concentrations of corticosterone. Trunk blood was collected into ice-cooled tubes containing 5% EDTA and centrifuged (2500 rpm, 4 °C, 15 min). Plasma was separated and stored at −30 °C until assayed for corticosterone. Plasma concentrations of corticosterone were measured using a commercially available kit for rats (^{125}I-corticosterone radioimmunoassay, ICN, Biomedicals, USA). Inter- and intra-assay coefficients of variation were 6.5% and 4.4%, respectively. The antibody cross-reacted 100% with corticosterone and <0.5% with other steroids.

ANALYTICAL PROCEDURE FOR MEASUREMENT OF ATRIAL CATECHOLAMINES

Norepinephrine, epinephrine, dopamine and DOPAC were estimated in the right atrium of the rat by high pressure liquid chromatography with electrochemical detection (HPLC/ED, Waters Millipore, MA, USA). After decapitation, the chest was opened with a midsternal incision and the right atrium dissected and stored at −80 °C until assayed for catecholamines. The right atrium was weighed and placed immediately in a dry ice-cooled polypropylene vial and homogenized with a Polytron homogenizer (setting 5 for 30 s) in 1 ml of perchloric acid 0.1 mol $litre^{-1}$ containing EDTA 2.7 mmol $litre^{-1}$ and 3,4 dihydroxy-benzylamine (DHBA) 5 pg μl^{-1} (Waters, MA, USA) as internal standard. The homogenates were centrifuged (15 000 rpm, 4 °C, 15 min), the supernatant layer removed into a 1-ml syringe and filtered through a 0.22-μm GV (Millipore), and 10 μl of each sample injected into a 5-μm C_{18} reserve-phase column (Waters). Electrochemical detection was accomplished with a glassy carbon electrode set at a potential of +0.65 V *vs* the silver–silver chloride reference electrode. The mobile phase consisted of a 95:5 (v/v) mixture of water and methanol with sodium acetate 50 mmol $litre^{-1}$, citric acid 20 mmol $litre^{-1}$, 1-octyl-sodium sulphonate 3.75 mmol $litre^{-1}$, 9, di-n-butylamine 1 mmol $litre^{-1}$ and EDTA 0.135 mmol $litre^{-1}$, adjusted to pH 4.3. Flow rate was 0.9 ml min^{-1}. Chromatographic data were analysed with a Waters 740 date module integrator and quantified using the peak area ratio of the internal standard. Atrial content of catecholamines was expressed as ng g^{-1} wet weight of tissue.

ISOLATED RIGHT ATRIA PREPARATION

The right atrium was isolated and suspended in a 10-ml organ bath. Tyrode solution of the following composition (mmol $litre^{-1}$) was used: NaCl 136.9; KCl 5.0; $MgCl_2$ 1.05; $CaCl_2$ 1.8; NaH_2PO_4 0.4; $NaHCO_3$ 11.9; and glucose 0.5. The bathing solution was maintained at 37 °C, pH 7.4 and bubbled with 95% oxygen and 5% carbon dioxide. Each preparation was suspended under a resting tension of 0.5 g and equilibrated for 45 min before the start of the experiment. The right atrium was beating spontaneously and the frequency of contraction was measured using a force displacement transducer (Grass FT-03) and recorded on a Letica polygraph. Only preparations that had a stable basal frequency of contraction at the end of the stabilization period were accepted for study.

INDUCTION OF PHYSICAL DEPENDENCE *IN VITRO*

Concentration–response curves were constructed for naloxone 10^{-9}–10^{-5} mol $litre^{-1}$ from the right atria in rats treated chronically with morphine or placebo pellets. Concentration–response curves for D-naloxone (inactive isomer) were also constructed in both types of preparations. Concentrations of drugs were increased after a steady-state response had been attained with the previous concentration.

DRUGS

Pellets of morphine base (Alcaliber Labs., Madrid, Spain) or lactose were prepared by the Department of Pharmacy, Clinic Hospital (Madrid, Spain). Naloxone HCl (Merck, Sharp and Dome, Madrid, Spain) and D-naloxone HCl (Endo Inc. New York,

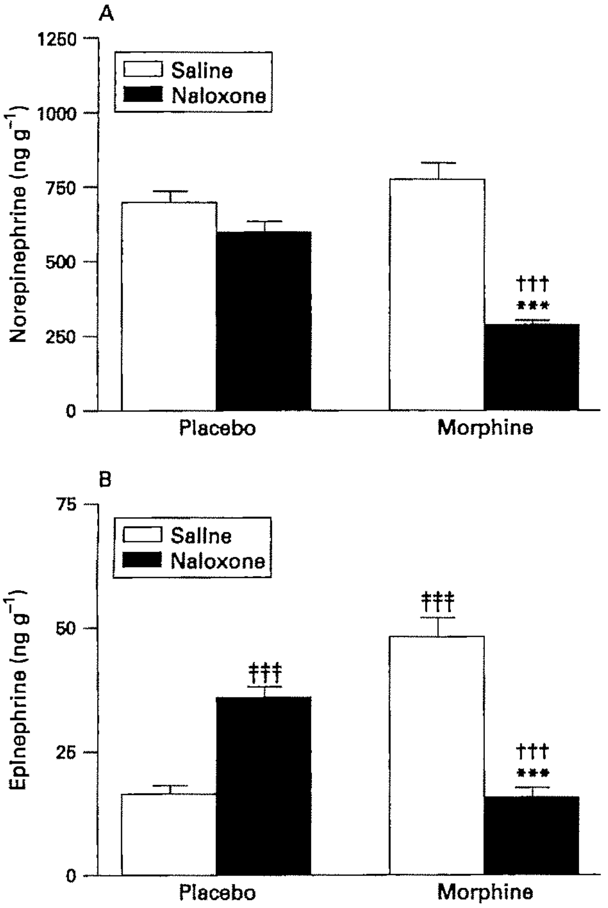

Figure 1 Atrial norepinephrine (A) and epinephrine (B) concentrations in placebo- and morphine-pelleted rats, 30 min after acute injection of saline s.c. or naloxone 1 mg kg^{-1} s.c. (mean (SEM) of 4–5 experiments). ***$P<0.001$ compared with morphine with saline; †††$P<0.001$ compared with placebo with naloxone; ‡‡‡$P<0.001$ compared with placebo with saline.

USA) were prepared fresh every day, dissolved in sterile 0.9% NaCl (saline) or distilled water, respectively. Other reagents were of HPLC grade.

STATISTICAL ANALYSIS

Data are expressed as mean (SEM). Statistical differences in the content of corticosterone, norepinephrine, epinephrine, dopamine, DOPAC and in the DOPAC/DA ratio were performed by two-way analysis of variance followed by the Newman–Keuls *post hoc* test. The results obtained *in vitro* were expressed as fractions of the change in the rate of contraction produced by a maximum dose of naloxone (mean (SEM) of *n* animals). In this case, statistical analysis was performed by one-way analysis of variance followed by the Newman–Keuls test. $P<0.05$ was considered significant.

Results

EFFECTS OF ACUTE NALOXONE ADMINISTRATION ON ATRIAL CATECHOLAMINE CONTENT AND CORTICOSTERONE RELEASE IN CHRONIC PLACEBO- OR MORPHINE-TREATED RATS

Acute administration of naloxone 1 mg kg^{-1} to morphine-treated animals decreased ($P<0.001$) atrial content of norepinephrine (290.2 (11.9) ng g^{-1}), epinephrine (15.6 (2.1) ng g^{-1}) and dopamine (9.52 (0.5) ng g^{-1}), whereas the DOPAC/DA ratio (1.38 (0.2)) increased ($P<0.001$) compared with the saline-injected group (norepinephrine 783.4 (52.2) ng g^{-1}; epinephrine 48.2 (3.6) ng g^{-1}; dopamine 37.2 (4.5) ng g^{-1}; and DOPAC/DA ratio 0.34 (0.04)). However, administration of naloxone to placebo-treated animals did not modify concentrations of norepinephrine (601.0 (27.1) ng g^{-1}), dopamine (27.6 (1.1) ng g^{-1}), DOPAC (24.9 (2.4) ng g^{-1}) or the DOPAC/DA ratio (0.9 (0.08)) but significantly ($P<0.001$) increased atrial content of epinephrine (35.6 (2.0) ng g^{-1}) compared with the respective control group injected with saline (figs 1, 2).

Plasma concentrations of corticosterone increased ($P<0.001$) 30 min after naloxone injection in morphine-treated rats (435.8 (27.6) ng ml^{-1}) compared with morphine-treated rats injected with saline (142.0 (17.5) ng ml^{-1}) or placebo-treated rats injected with naloxone (166.5 (13.3) ng ml^{-1}) (fig. 3). Plasma concentrations of corticosterone in placebo-treated rats injected with naloxone were similar to those in the respective control group given saline (168.5 (8.6) ng ml^{-1}).

EFFECTS OF NALOXONE ON ATRIAL RATE IN THE ISOLATED RIGHT ATRIA FROM CHRONICALLY PLACEBO- OR MORPHINE-TREATED RATS

In placebo-treated rats, naloxone 10^{-11}–10^{-3} mol $litre^{-1}$ decreased the frequency of contraction in a concentration-dependent manner. The maximum effect was obtained at 10^{-4} mol $litre^{-1}$ (24 (0.9) %). In contrast, in morphine-treated rats, naloxone increased atrial rate in a concentration-dependent manner, producing a maximum effect of 30 (0.1) % at 10^{-4} mol $litre^{-1}$ (fig. 4A). The inactive isomer D-naloxone induced similar effects in placebo and morphine-treated rats. Thus D-naloxone produced a decrease in atrial rate at concentrations of 10^{-11}–10^{-3} mol $litre^{-1}$ in placebo- or morphine-treated rats. In both groups the maximum effect was 30 (1.2) % (fig. 4B).

Discussion

Different methods have been used in several studies to induce opioid tolerance–dependence. In the present study, the method of morphine pellet implantation and the schedule used were similar to those described previously,[16–18] which produce a high degree of tolerance to the effects of morphine in the central nervous system. Moreover, opioid tolerance and withdrawal syndrome can be demonstrated in isolated tissues, such as in myenteric plexus longitudinal muscle (MPLM) strips from guineapig.[17 19] However, few studies have been performed in cardiac tissues.[13 20] Hence the mechanisms involved in opioid dependence in the heart are poorly understood.

In the present study the concentration–response curves to naloxone on isolated right atria were constructed approximately 1 h after isolation of the tissue and were undertaken in tissues that were set up in opioid-free Tyrode's solution. No differences in the degree of dependence have been observed in preparations that were maintained in morphine or examined in the absence of the opioid.[21] However, experiments in tissues that were bathed in a solution

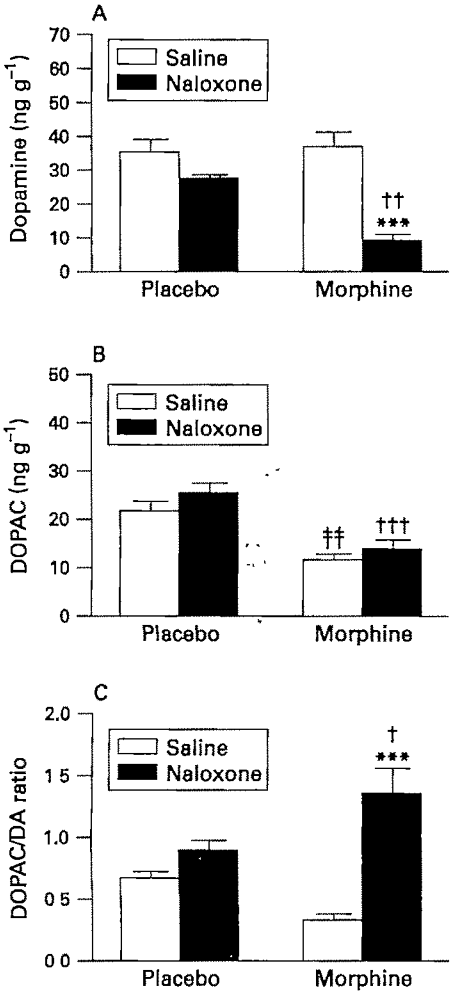

Figure 2 Atrial dopamine (A) and DOPAC (B) concentrations, and DOPAC/DA ratio (C) in placebo- and morphine-pelleted rats, 30 min after acute injection of saline s.c. or naloxone 1 mg kg^{-1} s.c. (mean (SEM) of 4–5 experiments) ***$P<0.001$ compared with morphine with saline; †$P<0.05$, ††$P<0.01$, †††$P<0.001$ compared with placebo with naloxone; ‡‡$P<0.01$ compared with placebo with saline.

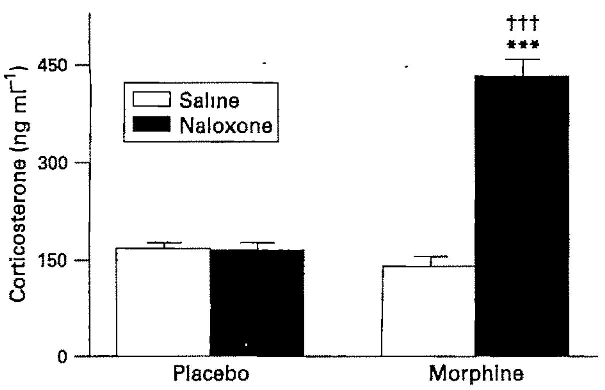

Figure 3 Plasma concentrations of corticosterone in placebo- and morphine-pelleted rats, 30 min after acute injection of saline s.c. or naloxone 1 mg kg^{-1} s.c. (mean (SEM) of 6–8 experiments). ***$P<0.001$ compared with morphine with saline; †††$P<0.001$ compared with placebo with naloxone.

containing morphine were difficult to quantify and interpret as the magnitude of the inhibitory effects produced by the maintenance concentration were unknown and therefore the degree of tolerance was also imprecise.[22]

In our study administration of naloxone to morphine-treated rats caused behavioural signs and symptoms of opioid withdrawal, such as wet-dog shakes, diarrhoea, escape jumps, teeth chattering, salivation, ptosis and irritability (data not shown). Moreover, our data showed that in morphine-treated rats, acute administration of naloxone decreased atrial content of norepinephrine, epinephrine and dopamine, whereas the ratio DOPAC/DA (an index of dopamine turnover) was increased. As expected, a large corticosterone response was observed after naloxone-induced withdrawal.

The mechanical response to naloxone in isolated right atria was different in preparations from naïve and tolerant rats. Thus in preparations from morphine-treated rats, naloxone induced a dose-dependent increase in heart rate whereas in preparations from placebo-treated rats, naloxone decreased this variable. In contrast, D-naloxone decreased the frequency of contraction in preparations from placebo- and morphine-treated rats. As D-naloxone is an inactive isomer, the decrease in the frequency of contraction obtained in our study was unlikely to be mediated via the opioid receptor. There is clear evidence that one of the autonomic symptoms of the withdrawal syndrome is tachycardia. This response could result from release of catecholamines in cardiac tissue. In addition, our results showed that chronic morphine treatment produced neuroendocrine physical dependence, as evidenced by an increase in corticosterone secretion 30 min after naloxone injection.

Several studies of opioid dependence in the central nervous system demonstrated that precipitation of withdrawal by administration of opioid antagonists to morphine-dependent rats caused an increase in firing of norepinephrine neurones in the locus coeruleus and an increase in the turnover of norepinephrine in the forebrain, in addition to a behavioural syndrome that has been associated with these effects.[5,6] Many symptoms of the autonomic nervous system which may be caused both by increasing activity of the locus coeruleus and by increased activity of spinal centres controlling sympathetic outflow.[23] In addition, chronic administration of opioids has been shown to increase concentrations of cAMP-dependent protein kinase and substrates for protein kinase, including tyrosine hydroxylase[24] (the rate-limiting enzyme in the biosynthesis of catecholamines) in the locus coeruleus. Moreover, studies in our laboratory have demonstrated that naloxone administration to tolerant rats enhanced plasma concentrations of corticosterone simultaneously with a reduction in hypothalamic content of norepinephrine.[11,12] As the paraventricular nucleus is a major area governing the output of the autonomic nervous system and ACTH secretion, the increase in corticosterone production and changes in heart catecholaminergic activity observed in our study can be attributed to a blunted response in the paraventricular nucleus.

Despite substantial evidence that noradrenergic neurones in the locus coeruleus and their projection to the hypothalamus are involved in opioid dependence and withdrawal,[4,14] there are few reports on the characteristics of functional disturbances of heart catecholaminergic neurones during opioid tolerance and dependence. Previous studies[14,15,24] have demon-

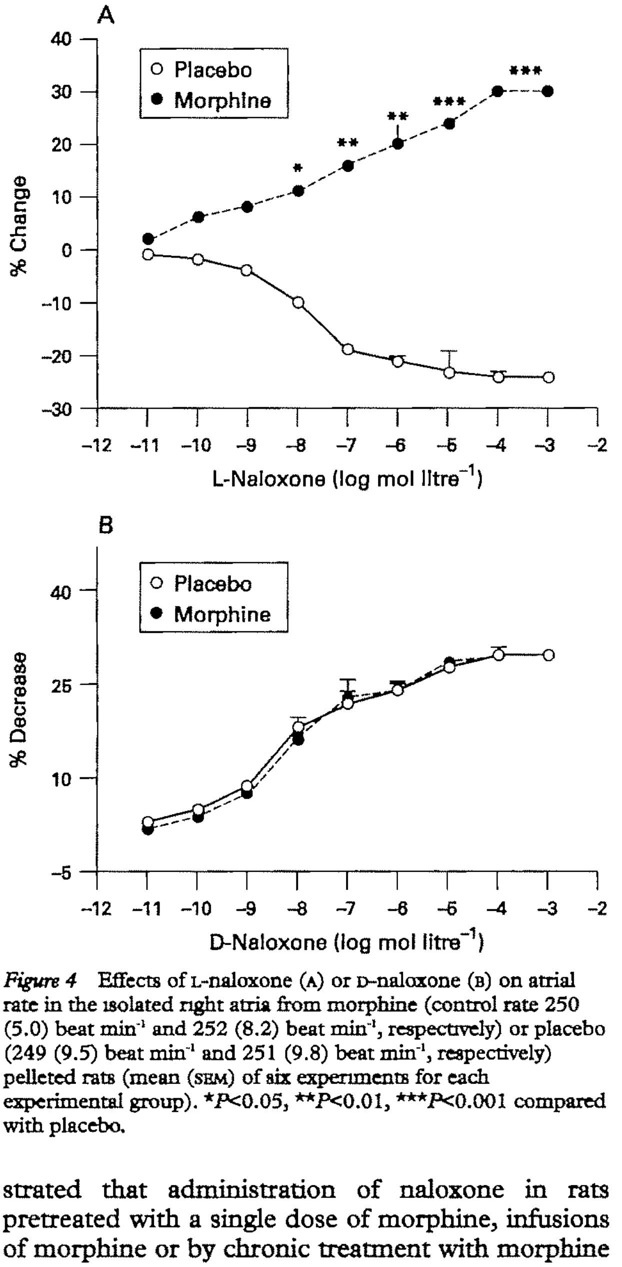

Figure 4 Effects of L-naloxone (A) or D-naloxone (B) on atrial rate in the isolated right atria from morphine (control rate 250 (5.0) beat min^{-1} and 252 (8.2) beat min^{-1}, respectively) or placebo (249 (9.5) beat min^{-1} and 251 (9.8) beat min^{-1}, respectively) pelleted rats (mean (SEM) of six experiments for each experimental group). *$P<0.05$, **$P<0.01$, ***$P<0.001$ compared with placebo.

strated that administration of naloxone in rats pretreated with a single dose of morphine, infusions of morphine or by chronic treatment with morphine pellets precipitated a withdrawal response, including an increase in mean arterial pressure, biphasic heart rate response and an increase in plasma concentrations of norepinephrine and epinephrine, suggesting that cardiovascular abstinence is mediated mostly by the catecholaminergic systems. Our results demonstrated clearly that catecholamines play an important role in the sympathetic manifestations of the abstinence response as naloxone induced a decrease in catecholamine content with an increase in dopamine turnover, which were accompanied by enhanced frequency of contraction.

However, parallel studies in guineapig ileum MPLM demonstrated that naloxone-induced withdrawal is characterized by contracture of the MPLM from morphine-treated animals.[17] Our results extend the findings in the MPLM to a different animal species, to a different physiological integrative level and to a different chain of neurotransmitter systems.

In summary, we have provided evidence that the abstinence syndrome is characterized by activation of catecholaminergic neurones in the heart that is accompanied by an increase in heart rate. We hypothesize that catecholaminergic pathways are involved in the hyperactivity of the autonomic nervous system associated with opioid withdrawal.

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Surfactant impairment after mechanical ventilation with large alveolar surface area changes and effects of positive end-expiratory pressure

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Summary

We have assessed the effects of overinflation on surfactant function and composition in rats undergoing ventilation for 20 min with 100% oxygen at a peak inspiratory pressure of 45 cm H_2O, with or without PEEP 10 cm H_2O (groups 45/10 and 45/0, respectively). Mean tidal volumes were 48.4 (SEM 0.3) ml kg^{-1} in group 45/0 and 18.3 (0.1) ml kg^{-1} in group 45/10. Arterial oxygenation in group 45/0 was reduced after 20 min compared with group 45/10 (305 (71) *vs* 564 (10) mm Hg); maximal compliance of the P–V curve was decreased (2.09 (0.13) *vs* 4.16 (0.35) ml cm H_2O^{-1} kg^{-1}); total lung volume at a transpulmonary pressure of 5 cm H_2O was reduced (6.5 (1.0) *vs* 18.8 (1.4) ml kg^{-1}) and the Gruenwald index was less (0.22 (0.02) *vs* 0.40 (0.05)). Bronchoalveolar lavage fluid from the group of animals who underwent ventilation without PEEP had a greater protein concentration (2.18 (0.11) *vs* 0.76 (0.22) mg ml^{-1}) and a greater minimal surface tension (37.2 (6.3) *vs* 24.5 (2.8) mN m^{-1}) than in those who underwent ventilation with PEEP. Group 45/0 had an increase in non-active to active total phosphorus compared with non-ventilated controls (0.90 (0.16) *vs* 0.30 (0.07)). We conclude that ventilation in healthy rats with peak inspiratory pressures of 45 cm H_2O without PEEP for 20 min caused severe impairment of pulmonary surfactant composition and function which can be prevented by the use of PEEP 10 cm H_2O. (*Br. J. Anaesth.* 1998; **80**: 360–364)

Keywords: ventilation, mechanical; ventilation, positive end-expiratory pressure; lung, damage; lung, surfactant; rat

Pioneering work by Mead and Collier in 1959 showed that mechanical ventilation in dogs resulted in a progressive decrease in pulmonary compliance which was reversed by periodic forced inflations.[1] Greenfield, Ebert and Benson related these changes in compliance to pulmonary surfactant by demonstrating increased surface tension in lung extracts from dogs whose lungs were ventilated with peak inspiratory pressures of 28–32 cm H_2O for 1–2 h.[2]

Intra-alveolar oedema in healthy rats subjected to intermittent positive pressure ventilation (IPPV) at high inflation pressures (HIPPV), without positive end-expiratory pressure (PEEP), was first demonstrated by Webb and Tierney[3] and later confirmed by Dreyfuss and colleagues.[4] Dreyfuss and colleagues showed that damage to lung tissue resulting in oedema formation began at the capillary endothelium and progressed rapidly to the alveolar epithelium within 20 min.[4] Using PEEP 10 cm H_2O and the same peak inspiratory pressure, the lung was partially preserved from this high permeability oedema.[4 5] A subsequent study showed that the main determinant of lung oedema formation was end-inspiratory lung volume and attributed the effect of PEEP to a decrease in lung capillary hydrostatic pressure.[6]

We postulate a different explanation for the effect of PEEP which may prevent impairment of the pulmonary surfactant system by reducing the large changes in alveolar surface area which occur during mechanical ventilation with large tidal volumes. The balance of hydrostatic forces is altered when surfactant is impaired: pressure within the alveolar fluid lining is reduced, applying more "suction" to the interstitial space. If PEEP reduces surfactant impairment, this prevents suction-induced pulmonary oedema. To assess this hypothesis, we conducted a study to measure changes in surfactant function and composition after mechanical ventilation with high lung volumes or with PEEP when changes in lung volume were less.

Materials and methods

The study was approved by the local Animal Committee, and the care and handling of the animals conformed with European Community guidelines (86/609/EC).

Twenty-four adult male Sprague–Dawley rats, weighing 290–350 g, were anaesthetized with 2% halothane and 65% nitrous oxide in oxygen, tracheotomized and a catheter inserted into a carotid artery. During the experiment anaesthesia was maintained with pentobarbital 60 mg kg^{-1} i.p. (Nembutal; Algin BV, Maassluis, the Netherlands); neuromuscular block was produced with pancuronium 2.0 mg kg^{-1} i.m. (Pavulon; Organon Technika, Boxtel, the Netherlands).

After neuromuscular block, the animals were connected to a ventilator (Servo Ventilator 300, Siemens-Elema, Solna, Sweden) in a pressure-controlled mode, at an ($F_{I_{O_2}}$) of 1.0, frequency 30 bpm and an I/E ratio of 1:2. In order to re-open the

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Table 1 Tidal volume (V_T) (ml kg^{-1}), mean arterial pressure (MAP) (mm Hg) and blood-gas tensions (torr) in the three groups who underwent ventilation during the study (mean (SEM)). Inter- and intra-group comparisons: ANOVA with Bonferroni post-test if ANOVA $P<0.05$. Significance difference compared with: #t=0 min: ‡t=1 min; §t=1, 10 min; *group 7/0; and †group 45/0

	Time (min)	Group 7/0	45/10	45/0
V_T	0	12.2 (1.2)	18.2 (2.2)*†	46.4 (2.7)*
	1	12.2 (1.2)	17.8 (2.1)*†	49.5 (2.7)*
	5	11.5 (1.0)	17.9 (2.7)*†	51.0 (2.1)*
	10	10.4 (1.3)#	18.5 (2.7)*†	49.6 (2.2)*
	15	10.2 (1.3)#	18.9 (2.7)*†	46.3 (2.5)*
	20	10.2 (1.2)#	18.9 (2.7)*†	44.9 (2.6)*
Pa_{O_2}	1	522 (18)	511 (18)	492 (12)
	10	497 (16)	525 (13)	524 (17)
	20	508 (24)†	564 (10)†‡	305 (71)§
Pa_{CO_2}	1	35.3 (3.3)†	31.5 (1.9)	23.4 (1.9)
	10	37.6 (3.8)†	42.0 (3.1)†	21.1 (1.8)
	20	39.6 (4.3)†	43.1 (3.8)†‡	24.8 (1.7)
MAP	0	113.1 (5.2)	97.0 (9.4)	103.5 (10.9)
	1	134.8 (5.7)	65.2 (7.9)*	77.3 (9.3)*
	10	136.5 (7.7)	85.4 (8.6)*	92.3 (5.8)*
	20	137.6 (5.8)	97.6 (15.3)	64.7 (8.1)*

Table 2 Recovery of lavage fluid and post-mortem data for maximal compliance (*C*max), Gruenwald index, V_5, total lung weight, total phosphorus, protein concentration of BAL and surface tension in all four groups after the ventilation period (mean (SEM)). Inter-group comparisons: ANOVA with Bonferroni post-test if ANOVA $P<0.05$. *Group 45/0 significantly different compared with all other groups

	Group Control	7/0	45/10	45/0
Recovery BAL fluid (%)	74.4 (1.9)	75.6 (2.2)	75.0 (3.2)	73.3 (1.2)
*C*max (ml cm H_2O^{-1} kg^{-1})	4.11 (0.23)	4.49 (0.48)	4.16 (0.35)	2.09 (0.13)*
Gruenwald index	0.41 (0.04)	0.46 (0.08)	0.40 (0.05)	0.22 (0.02)*
V_5 (ml kg^{-1})	17.0 (1.5)	16.0 (0.8)	18.8 (1.4)	6.5 (1.0)*
Total lung weight (g)	1.9 (0.1)	2.0 (0.1)	2.5 (0.1)	3.9 (0.1)*
Total phosphorus (μmol)	3.8 (0.9)	3.6 (0.3)	4.5 (0.2)	3.1 (0.3)
Protein concn BAL (mg ml^{-1})	0.44 (0.18)	0.30 (0.06)	0.76 (0.22)	2.18 (0.11)*
Minimal surface tension (mN m^{-1})	24.3 (1.3)	26.6 (1.8)	24.5 (2.8)	37.2 (6.3)*

atelectatic lung areas induced by the surgical procedure, mechanical ventilation with a peak airway pressure of 26 cm H_2O and a PEEP of 6 cm H_2O was applied for 30 s. The animals were allocated randomly to one of four groups (n = 6 in each group). Animals in group 7/0 underwent ventilation with a peak pressure of 7 cm H_2O without PEEP; group 45/0 underwent ventilation with a peak pressure of 45 cm H_2O without PEEP; and group 45/10 underwent ventilation with a peak pressure of 45 cm H_2O and a PEEP of 10 cm H_2O. Ventilatory frequency was set at 60 bpm in group 7/0 and 25 bpm in group 45/10 to maintain (Pa_{CO_2}) within the normal range. Ventilatory frequency in group 45/0 was the same as in group 45/10. The control group was killed immediately after the surgical procedure without undergoing mechanical ventilation. After ventilation for 20 min, the other animals were killed by an overdose of pentobarbital via the penile vein, followed by KCl.

Blood samples obtained from the carotid artery were measured (ABL 505, Radiometer, Copenhagen, Denmark) 1, 10 and 20 min after 30 s of ventilation with pressures of 26/6. Mean arterial pressure was measured using a Statham P23XL transducer (Spectramed, Oxnard, CA, USA) and recorded (Siemens Sirecust 404–1, Danvers, MA, USA).

During mechanical ventilation, animals were placed in a volume-constant body plethysmograph to allow continuous recording of tidal volume. A pressure transducer (Validyne model DP 45–32, Validyne Engineering Co., Northridge, CA, USA) recorded pressure changes which were sampled at 10 Hz using a 12-bit analogue-to-digital converter (DAS 1800, Keithley MetraByte, Taunton, MA, USA).

After the animals were killed, a static pressure–volume plot was recorded using conventional techniques.[7] Maximal compliance (*C*max) was defined as the steepest part of the pressure–volume deflation curve,[8] and was determined separately for each animal. The Gruenwald index, defined as $(2V_5 + V_{10})/2V\text{max}$, where V_5, V_{10} and Vmax = lung volumes above functional residual capacity (FRC) at transpulmonary pressures of 5, 10 and 35 cm H_2O, respectively, was calculated.[9] FRC was taken to be total lung volume at a transpulmonary pressure of 5 cm H_2O (V_5)[10] ; total lung weight was recorded. The lungs were lavaged with saline–$CaCl_2$ 1.5 mmol litre^{-1}.[11] The active component of surfactant in the bronchoalveolar lavage fluid was separated from the non-active surfactant component by differential centrifugation[11] followed by subsequent phosphorus analysis,[12] and the ratio of inactive to active surfactant was calculated. The protein concentration of BAL was determined using the Bradford method (Bio-Rad protein assay, Munich, Germany).[13] Some of the re-suspension (20 μl) of the active surfactant part was used for biophysical analysis of minimal surface tension after 50 cycles on a pulsating bubble surfactometer (PBS; Electronetics Corporation, Tonowanda, NY, USA), as described by Enhorning.[14]

STATISTICAL ANALYSIS

Statistical analysis was performed using the Instat 2.0 biostatistics package (GraphPad software, San Diego, CA, USA). Intra-group comparisons were analysed using ANOVA. Inter-group comparisons were analysed with repeated measures ANOVA. If ANOVA resulted in $P < 0.05$, a Bonferroni post-test was performed. All data are reported as mean (SEM).

Results

Data followed a normal distribution. Tidal volume, (Pa_{O_2}), (Pa_{CO_2}) and mean arterial pressure over time in the three groups are shown in table 1. During the study, tidal volumes differed markedly between groups (table 1). At t = 1 min, (Pa_{O_2}) was comparable in the three study groups and remained stable in groups 7/0 and 45/10; (Pa_{O_2}) in group 45/0 decreased significantly after 10 min.

Table 2 shows recovery of BAL fluid and post-mortem data for *C*max, Gruenwald index, V_5, total lung weight, total phosphorus, protein concen-

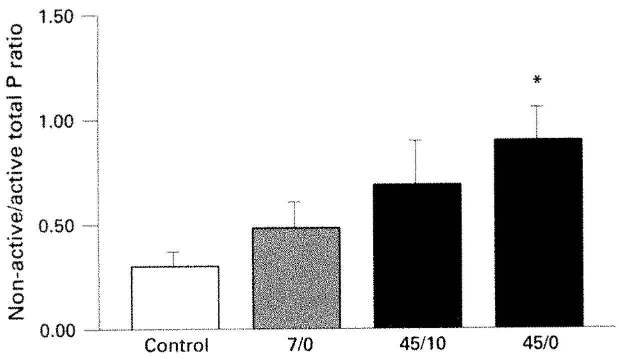

Figure 1 Ratio of non-active to active total phosphorus (P). Group 45/0 had a significant conversion of active to non-active total P during the ventilation period compared with controls. Values are mean (SEM). $*P < 0.05$ compared with the control group.

tration of BAL and minimal surface tension for the three study groups and the control group. There was no significant difference between group 7/0 and the control group for any variable. However, there were significant differences between group 7/0 and group 45/0 for all variables except total phosphorus. Figure 1 shows that the ratio of non-active to active surfactant was greater in group 45/0 compared with controls. Group 45/10 showed no impairment of any variable compared with the other groups or with controls. In addition, all variables were significantly different between groups 45/10 and 45/0.

Discussion

In this study we used an established rat model of ventilation-induced lung injury first developed by Webb and Tierney[3] and later investigated by Dreyfuss and colleagues.[4 5] The role of changes in pulmonary surfactant, however, has never been investigated in this animal model. The study was designed to better understand the relation between changes in lung morphology and permeability, and changes in the pulmonary surfactant system. We used established techniques to characterize the pulmonary surfactant system. Significant changes in surfactant function and composition occurred after lung overinflation without PEEP for a period as short as 20 min. Surfactant composition, characterized by significant conversion of active to non-active surfactant, was changed after ventilation with HIPPV, without PEEP, compared with controls who did not undergo ventilation. Impairment of surfactant function after lung overinflation was associated with impairment of lung mechanics and an increase in minimal surface tension of lung lavage fluid extracts. Impairment of surfactant composition and function caused by lung overinflation was prevented by the use of PEEP 10 cm H_2O. These findings support the hypothesis that the beneficial effect of PEEP in this model of ventilation-induced lung injury is mediated by prevention of impairment of surfactant composition and function.

Protein concentration after mechanical ventilation with high lung volumes was increased in BAL fluid in group 45/0; PEEP 10 cm H_2O prevented protein accumulation. These data are consistent with previous studies in this model which showed less accumulation of lung water, lung protein permeability and absence of intra-alveolar oedema with PEEP 10 cm H_2O during ventilation with high peak inspiratory lung volumes.[3 5]

The exact mechanism of ventilation-induced lung injury, and contributory factors, are still disputed. Experiments in rats with high peak inspiratory pressure ventilation of 45 cm H_2O, where peak inspiratory volume was limited by thorax restriction, have shown clearly that high peak inspiratory pressures alone do not induce lung injury.[5] However, a high peak inspiratory lung volume with peak inspiratory overstretching alone can also not explain ventilation-induced lung injury, as the use of PEEP 10 cm H_2O at identical peak inspiratory lung volumes almost completely prevented histologically assessed lung injury.[5] Although a role for surfactant in lung injury caused by lung overinflation was suggested,[5] our data are the first to show the association of surfactant changes in lung injury with mechanical ventilation using high lung volumes.

Several mechanisms are involved in the changes in surfactant function during mechanical ventilation. First, mechanical ventilation combined with overinflation enhances the release of surfactant from pneumocytes type II into the alveolus.[15-18] This material may be lost from the alveoli into the airways by compression of the surfactant film if the alveolar surface area becomes smaller than the surface area occupied by the surfactant molecules, so that surface-active material moves into the airways.[19 20] This mechanism of surfactant depletion after mechanical ventilation was first shown by Faridy in the isolated rat lung.[20] Mechanical ventilation increased the surface activity of lavage fluid of the pulmonary airways; this change in activity was dependent on the duration of ventilation and size of the tidal volume.[20] Studies by Wyszogrodski and colleagues have shown that PEEP prevents a decrease in lung compliance and surface activity of lung extracts, indicating prevention of loss of alveolar surfactant function during lung overinflation.[19] It was suggested that PEEP prevents alveolar collapse and thus maintains the end-expiratory volume of alveoli at a higher level, thereby preventing excessive loss of surfactant in the small airways during expiration.[21]

Second, the pulmonary surfactant system can be divided into active and non-active subfractions by differential centrifugation.[11] The active subfractions, which represent tubular, myelin-like forms of surfactant, are the metabolic precursors of the non-active components, which represent small vesicular structures.[22] Gross and Narine were the first to show that conversion of active to non-active surfactant subfractions is dependent on cyclic changes in surface area *in vitro*.[23] To maintain an adequate pool of functional surfactant subfractions in the airspaces *in vivo*, it is necessary to maintain a balance between secretion, uptake and clearance of the active and non-active surfactant subfractions.[22] Recent *in vivo* studies by Veldhuizen and colleagues in rabbits attributed surfactant conversion to a change in alveolar surface area associated with mechanical ventilation.[24 25] They found that changing ventilatory frequency[24] or the level of PEEP[25] did not affect the rate of conversion but that conversion of surfactant subfractions is dependent on tidal volume and time.[24] We found a significant conversion of active to non-active surfactant in group 45/0 compared with non-ventilated controls, but no significant conversion in the two other groups who underwent ventilation compared with controls. We suggest that the large tidal volume in group 45/0 was able to induce significant surfactant conversion within 20 min. However, this 20-min period was too short to cause a significant difference in surfactant conversion in the groups undergoing ventilation with lower tidal volumes compared with non-ventilated controls. The exact mechanisms underlying surfactant conversion as a result of changes in surface area are unknown.

An important function of pulmonary surfactant is to aid fluid balance in the lung and prevent pulmonary oedema from increased suction forces at the alveolo-capillary barrier.[26] Loss of surfactant function with an increase in surface tension at the air–liquid interphase on the alveolar walls decreases the pressure in the alveolar fluid, altering the pressure gradient across the alveolo-capillary membrane in the alveolar direction.[26–28] *In vitro* and *in vivo* studies have shown that pulmonary oedema, and in particular plasma-derived proteins in this oedema, are capable of inactivating surfactant in a dose-dependent manner.[29–32] This further decreases the pressure in the alveolar fluid and thus causes further surfactant inactivation. When this vicious circle of surfactant inactivation has started, the resulting protein-rich pulmonary oedema accounts for much of the surfactant alterations seen in group 45/0. The importance of subtle primary changes in the pulmonary surfactant system in increasing the pressure gradient across the alveolo-capillary membrane, initiating a subsequent cascade of protein inactivation, was recently shown in a model of surfactant perturbation by dioctyl sodium sulphosuccinate, which does not cause any other damage to the alveolo-capillary barrier.[28] The study also showed that changes in surfactant make the lung vulnerable to damage by mechanical ventilation.[28]

Findings in animals with induced acute respiratory failure and in patients with acute respiratory distress syndrome (ARDS) suggest that changes in the pulmonary surfactant system play a central role in this disease process.[33] Irrespective of the cause, decreased surfactant function increases the forces acting at the air–liquid interface of the alveolus and can lead to consequences such as decreased pulmonary compliance, decreased FRC with end-expiratory alveolar collapse, right-to-left shunt and hypoxaemia with anaerobic metabolism.[33] Such changes necessitate the use of mechanical ventilation to maintain adequate oxygen delivery to the tissues. Mechanical ventilation may, however, perpetuate the alterations in the pulmonary surfactant system, as found in this study, indicating that mechanical ventilation with high peak inspiratory pressures in patients with ARDS may impair the function of those alveoli that are still intact. The data also suggest that it is important to use PEEP in these patients to preserve normal surfactant function of alveoli that are not yet affected by the disease process.

We conclude that ventilation of the lungs of healthy rats with high peak inspiratory volumes at peak inspiratory pressure of 45 cm H_2O without PEEP caused severe impairment of pulmonary surfactant composition and function. PEEP prevented this impairment of the surfactant system, probably by reducing the amount of change in alveolar surface area, which prevents: surfactant displacement from the alveolar air–liquid interface into the small airways; increased conversion of active to non-active surfactant subfractions; and increased hydrostatic forces over the alveolo-capillary barrier which could lead to a self-propagating mechanism of surfactant inactivation.

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Effects of inhalation anaesthetics on the release of acetylcholine in the rat cerebral cortex *in vivo*

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Summary

By analysing the EEG, reticular multi-unit activity and behavioural changes, we have classified general anaesthetics into three groups: central nervous system (CNS) depressant, CNS excitant and epileptogenic agents. Changes in CNS neural activity are associated with alteration in transmitter release. We have attempted to clarify the actions of widely used inhalation anaesthetics, such as isoflurane (CNS depressant), nitrous oxide (CNS excitant) and sevoflurane (epileptogenic) on acetylcholine (ACh) release in the cerebral cortex using brain microdialysis. ACh release was suppressed by isoflurane and sevoflurane in a dose-related manner but recovered on wash-out. There were no significant differences between the effects of sevoflurane and isoflurane at the same MAC values. In contrast, ACh release was enhanced significantly by nitrous oxide. These findings indicate that the response of the cortical cholinergic cells to different anaesthetics reflects their neurophysiological characteristics, that is whether they stimulate or suppress CNS neurones.

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Keywords: anaesthetics volatile, sevoflurane; anaesthetics volatile, isoflurane; anaesthetic gases, nitrous oxide; parasympathetic system, acetylcholine; brain, cerebral cortex; rat

Acetylcholine (ACh) is one of the major excitatory neurotransmitters in the central nervous system (CNS). The activity of cholinergic neurones has long been postulated to play a key role in regulating the state of consciousness, and it has been shown that cortical ACh release decreases in the transition from wakefulness to sleep.[1] Zucker confirmed that depression of central cholinergic neurones by hemicholinium-3 and oxotremorine reduced the MAC of isoflurane and, conversely, that facilitation by physostigmine increased the MAC of isoflurane.[2]

Based on CNS electrical activities, our laboratory has classified general anaesthetics into three categories: CNS depressant, CNS excitant and epileptogenic anaesthetics.[3 4] The CNS depressant anaesthetics induced irregular alpha range slow waves (type I slow waves), the so-called barbiturate spindle bursts, which were associated with a decrease in spontaneous firing of reticular neurones. Barbiturates, halothane, methoxyflurane[4] and isoflurane[5] are members of this category. The CNS excitant anaesthetics induced rhythmic sine-curve slow waves in the theta and delta range (type II slow waves). These types of slow waves were associated with an increase in spontaneous firing of reticular neurones. Nitrous oxide, diethyl ether, cyclopropane and ketamine are included in this category.[4] With the exception of nitrous oxide, the type II slow waves were followed, not by a flattening but by a generalized electrographic, non-convulsive, high frequency, high amplitude, seizure-type activity in extremely deep planes. The epileptogenic agents resulted in type I slow waves, which were associated with a decrease in spontaneous firing of reticular neurones in light, non-convulsive planes, and spikes and electrical silence in deep, convulsive planes. The EEG spikes were associated with a phasic increase in the firing of reticular neurones, myoclonic jerking and the generalized high amplitude, high frequency activity of the seizure type, with a sustained increase in the firing of reticular neurones and generalized convulsions. Sevoflurane,[6] enflurane and gamma-hydroxybutyrate[4] are members of this category.

Using an *in vivo* microdialysis technique, we attempted to clarify the role of cholinergic neurones in the cerebral cortex during anaesthesia. One representative anaesthetic from each group was studied, that is isoflurane, sevoflurane and nitrous oxide. The development of acute tolerance to the CNS actions of nitrous oxide has been reported by us[3 7–9] and by others.[10–13] Therefore, we have also attempted to confirm if tolerance to nitrous oxide involves cortical cholinergic neurones.

Materials and methods

BRAIN DIALYSIS

The study was approved by the Animal Research Committee of Kyoto University Faculty of Medicine. We used 35 male Wister rats, weighing 250–300 g. They were housed, one per cage, under a 12-h light–dark cycle (lights on from 07:00 to 19:00) with free access to food and water. All experiments were started between 10:00 and 11:00. The animals were

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anaesthetized with pentobarbital 50 mg kg^{-1} i.p. and placed on a stereotaxic frame. The skull was exposed through a midline incision of the scalp and a burr hole of 3-mm diameter was drilled. A cannula was implanted in the frontal cortex at A 3.0 mm and L 2.0 mm from the bregma, according to Paxinos and Watson,[14] and was 2.0 mm in depth. The cannula was fixed to the skull with dental cement and a stainless steel screw. The location of the probe was confirmed by visual examination of the brain at the end of each experiment. The animals were allowed to recover for at least 1 day. On the day of study, the stylet was removed from the cannula and a microdialysis probe inserted. Rats were placed in clear plastic boxes (20 × 15 × 15 cm) which were gassed continuously with 75% nitrogen and 25% oxygen (3 litre min^{-1} and 1 litre min^{-1}, respectively). The dialysis probe was connected to the perfusion pump and sample loop of an automated sample injector (model 10; EICOM, Kyoto, Japan) using polyethylene tubing. The internal standard, ethylhomocholine, delivered by the perfusion pump, was connected into the perfusate tube proximal to the injection valve. The dialysis probe was perfused continually with Ringer solution (Na^+ 147 mmol $litre^{-1}$, Ca^{2+} 2.3 mmol $litre^{-1}$, K^+ 4 mmol $litre^{-1}$, Cl^- 156 mmol $litre^{-1}$, pH 6.0) containing physostigmine 10 μmol $litre^{-1}$ at a rate of 2.0 μl min^{-1}.

Perfusate samples obtained during the first 2 h after implantation of the probe were discarded. The dialysates were then collected every 20 min in the sample loop of the automated sample injector, which was on line to an HPLC system. As analysis of ACh was complete within 20 min, the sample loop was set to be held in the load position for 20 min and was switched automatically to the injection position for 60 s, after which the cycle was repeated.

ADMINISTRATION OF ANAESTHETICS

The rats were divided into three groups for different studies.

(1) Comparison of isoflurane and sevoflurane

After 1 h of control dialysate collection, 0.5 MAC (0.75%) of isoflurane was added to the nitrogen–oxygen gas mixture for 1 h. Subsequently, the concentration of isoflurane was increased to 1.0 MAC (1.5%) and then 1.5 MAC (2.25%), with a 1-h equilibration period. One hour after discontinuation of isoflurane, 0.5 MAC (1.1%), 1.0 MAC (2.2%) and 1.5 MAC (3.3%) of sevoflurane were given for 1 h. MAC values of 2.20% sevoflurane and 1.52% isoflurane were as reported previously.[15] [16] These experiments were carried out in eight rats (group a), and then isoflurane and sevoflurane were given in reverse order to seven rats (group b). As stated below, there were no significant differences between groups a and b (data not shown), and the results from the two groups were combined.

(2) Comparison of the three anaesthetics

Ten rats were used. After 1 h of control dialysate collection, 0.3 MAC (0.7%) of sevoflurane was added to the nitrogen–oxygen mixture for 1 h and then sevoflurane was discontinued. In the same way, 1 h after stopping sevoflurane, 0.3 MAC (0.5%) of isoflurane was added for 1 h and then discontinued. One hour later, 75% nitrogen was replaced with nitrous oxide (0.3 MAC)[17] for 1 h, and then returned to the control gas mixture for 1 h.

(3) Study of long-term exposure to nitrous oxide

Ten rats were used. After 1 h of control dialysate collection, nitrogen was replaced with nitrous oxide for 4 h and then returned to the control gas mixture for 2 h.

All anaesthetics, oxygen and carbon dioxide concentrations in the box were monitored by an anaesthetic gas monitor (Type 1304; Brel and Kjaer, Denmark). Both sevoflurane and isoflurane reached expected concentrations and decreased to less than 0.1% within 5 min. Nitrous oxide reached expected concentrations and decreased to less than 2.0% within 8 min. The behaviour of the animals was observed throughout the experiments.

ACh ASSAY

ACh in the dialysates was measured using HPLC combined with an immobilized enzyme reactor and electrochemical detector, according to the method by Damsma, Westerink and Horn.[18] In brief, an Eicompak AC-Gel column (6 × 150 mm; EICOM, Japan) was used for separation. An enzymatic reactor containing acetylcholinesterase and choline oxidase, covalently attached to aminopropyl-controlled pore glass, converted ACh to hydrogen peroxide, which was detected by an electrochemical detector with a platinum electrode (model 100; EICOM) at 450 mV. The mobile phase was delivered by a pump (EP-10, EICOM) at 1.0 ml min^{-1} and contained sodium phosphate buffer 0.1 mol $litre^{-1}$ (pH 8.0), sodium 1-decansulphonate 200 mg $litre^{-1}$ and tetramethylammonium chloride 65 mg $litre^{-1}$. Quantification of the collected ACh was performed by comparison with the internal standard (ethylhomocholine) peak area.

STATISTICAL ANALYSIS

In all studies, experimental stability was confirmed by comparison of the mean initial three dialysate collections. When stability was confirmed, this served as a basal value for succeeding drug studies. When isoflurane and sevoflurane were compared, the mean value immediately before the second drug exposure was compared with those of the initial three collections. When pre-drug values did not differ from the initial three collections, this was used as the basal value in the second drug study, and data were combined with those in the first drug study using the same drug. All data are expressed as percent of basal values and represent mean (SEM). In all studies, the results were assessed for statistical significance by analysis of variance (ANOVA) with repeated measures and, when significant *F* values were obtained, Fisher's protected least significant difference (PLSD) test was used for significant differences between

Table 1 Changes in perfusate ACh content after isoflurane (mean (SEM), n=12). P<0.05 compared: with [a]control; [b]both 20–40 and 40–60 min after isoflurane; [c]0–20 min of 0.5 MAC of isoflurane; and [d]both 40–60 min of 0.5 MAC and 40–60 min of 1.0 MAC of isoflurane

		Isoflurane concentration (MAC)			
Time (min)	Control (%)	0.5 (%)	1.0 (%)	1.5 (%)	0 (after isoflurane) (%)
0–20	—	74.1 (12.7)^{a}	30.1 (4.9)^{a,b,c}	18.8 (3.5)^{a,b,c,d}	32.3 (11.0)^{a,b,c}
20–40	—	32.7 (8.7)^{a,b,c}	28.5 (5.1)^{a,b,c}	14.5 (4.0)^{a,b,c,d}	76.5 (15.5)^{a}
40–60	100.0	44.8 (11.7)^{a,b,c}	42.7 (10.4)^{a,b,c}	15.7 (3.3)^{a,b,c,d}	98.5 (14.8)

Table 2 Changes in perfusate ACh content after sevoflurane (mean (SEM), n=12). P<0.05 compared with: [a]control; [b]both 20–40 and 40–60 min after sevoflurane; [c]both 0–20 and 40–60 min of 0.5 MAC of sevoflurane; and [d]both 0–20 and 20–40 min of 1.0 MAC of sevoflurane

		Sevoflurane concentration (MAC)			
Time (min)	Control (%)	0.5 (%)	1.0 (%)	1.5 (%)	0 (after sevoflurane) (%)
0–20	—	62.1 (7.9)^{a,b}	53.2 (11.5)^{a,b}	42.2 (12.7)^{a,b}	39.3 (9.3)^{a,b}
20–40	—	30.0 (7.8)^{a,b}	65.4 (16.8)^{a,b}	18.0 (4.6)^{a,b,c,d}	127.0 (13.6)
40–60	100.0	43.2 (9.3)^{a,b}	39.6 (12.4)^{a,b}	18.9 (4.9)^{a,b,c,d}	113.5 (20.0)

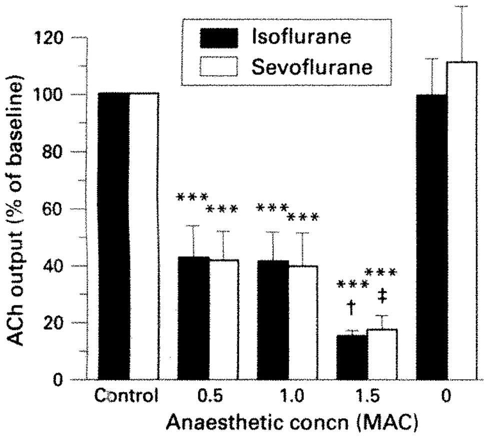

Figure 1 Effects of isoflurane and sevoflurane on ACh content in the dialysate. ACh in each fraction is expressed as a percentage of the values obtained from the collections immediately before administration of anaesthetic. Data are mean (SEM) (n = 12). $^{***}P < 0.001$ *vs* control and 0 MAC; †$P < 0.05$ *vs* 0.5 and 1.0 MAC; ‡P <0 .05 *vs* 0.5 MAC. There were no significant differences between isoflurane and sevoflurane.

treatment means. A probability level of $P < 0.05$ was considered significant.

Results

Data from eight rats (i.e. three used for comparison of isoflurane and sevoflurane, three for comparison of the three anaesthetics and two for the nitrous oxide tolerance test) were discarded because of unstable ACh release in the second or third fractions in the initial three collections by more or less than 30% of the first collection. The stability of the initial three collections of rats adopted for all drug studies was confirmed in that the differences in means of the three collections did not differ significantly. ACh content in these collections was 3.9 (0.6) pmol/20-min collection.

EFFECTS OF SEVOFLURANE, ISOFLURANE AND NITROUS OXIDE

Mean values of the initial three collections were 103.8 (4.8) %, 97.5 (8.0) % and 98.6 (9.2) % (ns). ACh release immediately before the second drug studies (93.1 (8.6) % for isoflurane and 87.0 (12.8) % for sevoflurane) did not differ significantly from those of the initial three collections for both anaesthetics. Therefore, the data were combined with those of the initial exposures. The changes in ACh release are summarized in table 1 for isoflurane and in table 2 for sevoflurane. Both anaesthetics significantly suppressed ACh release in a dose-related manner, with effects at 1.5 MAC being maximum. There were no significant differences between sevoflurane and isoflurane. ACh release was restored to control levels after discontinuation (see also fig. 1). In addition, after discontinuation of the first anaesthetic, the animals became alert, usually after 20 min, and then quiet and sleepy until the start of the second anaesthetic study, when they awoke, possibly in response to the pungency of the anaesthetic agent.

Changes in ACh release by equipotent doses of all anaesthetics and those in the recovery phases are summarized in table 3. Both sevoflurane and isoflurane suppressed ACh release significantly, and after discontinuation of both agents returned to pre-anaesthetic levels. Nitrous oxide increased ACh release significantly. After discontinuation, ACh release returned gradually, in 20–60 min, to levels not significantly different from basal. During inhalation of isoflurane and sevoflurane, animals remained still and quiet. In contrast, they became alert and moved around in response to nitrous oxide for

Table 3 Changes in perfusate ACh content after 0.3 MAC of sevoflurane, isoflurane and nitrous oxide (mean (SEM), n=7). $^{*}P$<0.05 compared with the value just before each anaesthetic administration

	Time (min)		
	0–20 (%)	20–40 (%)	40–60 (%)
Baseline	104.1 (6.9)	98.5 (7.9)	97.4 (5.2)
Sevoflurane	83.8 (8.4)	63.1 (10.1)*	59.6 (14.9)*
After sevoflurane	76.1 (5.1)	113.3 (14.8)	96.6 (9.6)
Isoflurane	86.6 (7.4)	61.9 (8.4)*	58.6 (7.8)*
After isoflurane	76.1 (5.8)	102.2 (15.2)	130.3 (15.7)
Nitrous oxide	158.8 (19.3)	193.7 (20.0)*	182.7 (13.8)*
After nitrous oxide	184.8 (21.8)*	133.8 (14.2)	136.5 (11.1)

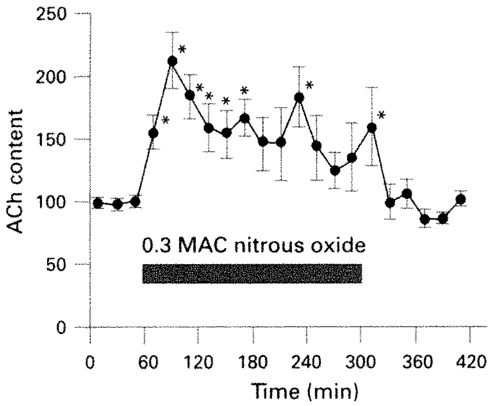

Figure 2 Effects of 0.3 MAC of nitrous oxide on ACh content in the dialysate. ACh in each fraction is expressed as a percentage of the mean of three initial collections. Data are mean (SEM) (n = 8). *P< 0.05 *vs* control.

approximately 30 min, then gradually became quiet. After discontinuation of anaesthesia, animals became alert within 5 min.

EFFECTS OF LONG-TERM EXPOSURE TO NITROUS OXIDE

Mean values of the initial three collections were 100.1 (3.0) %, 97.9 (4.3) % and 101.9 (4.3) % (ns). ACh release increased significantly to reach a maximum of 215.2 (21.0) % in the second fraction (20–40 min, $P < 0.001$), which was followed by a gradual decrease (fig. 2). After 120 min of exposure, there were no differences from the control values except for a transient increase in the ninth (160–180 min) and 13th (240–260 min) fractions. The animals became alert and moved around with inhalation of nitrous oxide for approximately 30 min, then gradually became quiet. The animals remained still and quiet for the last 180 min. After discontinuation of nitrous oxide, the animals became alert within 5 min.

Discussion

We have demonstrated that isoflurane and sevoflurane suppressed and nitrous oxide enhanced ACh release in the rat cerebral cortex. In addition, the gradual decline in the increase produced by nitrous oxide supports our hypothesis of the development of acute tolerance to this agent.

The MAC value for nitrous oxide in rats is 2.2–2.4 atm according to Gonsowski and Eger,[17] and 75% nitrous oxide in 1 atm corresponds to 0.3 MAC. This value for nitrous oxide was compared with the effects of equipotent doses, that is 0.3 MAC of isoflurane and sevoflurane, and it was confirmed that nitrous oxide enhanced ACh release while isoflurane and sevoflurane suppressed release. Our study is the first to demonstrate significant enhancement of cortical ACh release by nitrous oxide. In previous studies with other anaesthetics, Phillis reported greater rates of cortical ACh release by diethyl ether or halothane than pentobarbital or alpha-chloralose.[19] However, he did not study the dose–effect relationship, and no basis was provided for the comparison of different anaesthetics at similar depths. Recently, ketamine, another CNS excitant anaesthetic, was shown to enhance ACh release in the rat hippocampus.[20] However, the significance of this study in the hippocampus is not clear and not comparable with our study.

Decreases in striatal ACh release induced by chloral hydrate, pentobarbital and halothane were reported recently.[21 22] The significance of activities of the cholinergic cells projecting to the striatum is beyond the scope of this study. However, these agents belong to the category of CNS depressants in our classification, and their findings may have some similarity with our results. In our study, isoflurane, a depressant anaesthetic, and subconvulsive doses of sevoflurane, an epileptogenic agent, decreased ACh release in the cerebral cortex. In these two groups, the decrease in ACh release correlated with suppression of spontaneous neural activity in the CNS at non-convulsive planes of anaesthesia, suggesting that suppression of cholinergic activities is in part one of the cellular mechanisms of anaesthesia.

Although cholinergic neurones have been postulated to have key roles in the maintenance of consciousness,[1] and the rats in our study were quiet during exposure to nitrous oxide, ACh release was not suppressed but enhanced. This fact, however, does not necessarily argue against the so-called unitary theory of anaesthesia. Our view is that, although no basis is provided, the CNS neuronal network is highly integrated and intricate, and expression of anaesthetic actions may differ when different measures are used. Briefly, our view is that suppression of cortical cholinergic activity may correlate with suppression of consciousness, but the reverse is not always true and activation does not necessarily correlate with elevation in the level of vigilance.

Mori and Winters were the first to document the development of acute tolerance to nitrous oxide, based on CNS electrical activities and the wake–sleep cycle in cats.[3] This observation was followed by several reports of nitrous oxide tolerance in various brain functions in animals and humans, such as analgesic actions,[10 11 13 23 24] suppression of righting reflex,[12 25] EEG,[8] anticonvulsant actions,[7] changes in brainstem opioid receptor density,[26] activation of the dopaminergic system[9] and cortical evoked potential.[7 27 28] However, different brain functions may be affected by anaesthetics in different ways, and not all studies support the development of tolerance to all of the CNS actions of nitrous oxide.[29] The time course of the development of tolerance, if observed, varies from a few minutes[12] to more than 10 h.[11 26 28] In our studies in cats,[7] rats[9] and humans,[8] the maximum effects of nitrous oxide were observed during the first 30 min, subsiding gradually within 2 h, to reach a steady state. The time course of changes in ACh release in our study was consistent with our previous studies. However, further studies are required to determine if changes in ACh release are the cause or result of tolerance.

Previous electrophysiological studies have indicated that the CNS actions of nitrous oxide include stimulation, that is activation of reticular cell firing,[3 30] and excitation of preganglionic sympathetic fibres.[31] We have confirmed CNS excitation of cholinergic neurones by nitrous oxide. Hornbein and colleagues[32] demonstrated hyper-reactivity in human volunteers, for example catatonic jerking of the extremities during hyperbaric nitrous oxide anaesthesia (1.55 atm). Furthermore, they observed nausea and vomiting in all subjects after exposure to nitrous oxide. We have documented previously activation of the cortical and medullary dopaminergic systems in rats by nitrous oxide, and attributed activation of cortical dopaminergic cells to the euphoric action and that of the medulla to the nausea and emesis during and after short-term nitrous oxide administration.[9] Emesis is a process induced by activation of the vomiting centre in the lateral reticular formation of the medulla, which receives input from the chemoreceptor trigger zone (CTZ) in the medulla. The CTZ is richly endowed with receptors, not only for dopamine, but also for ACh.[33] We thus postulate that nitrous oxide stimulates central cholinergic and dopaminergic neuronal networks.

Several reports have suggested that delayed emergence from anaesthesia can be treated successfully with i.v. physostigmine.[34–41] Our study provides the basis for this treatment in the case of isoflurane and sevoflurane.

In summary, isoflurane and sevoflurane suppressed and nitrous oxide enhanced ACh release in the rat cerebral cortex *in vivo*. The release of ACh in this study reflects activation of cholinergic neurones projecting to the cortex and suggests that our classification of anaesthetics (CNS depressant and excitant) involves cholinergic neurones projecting to the cerebral cortex. The decrease in ACh release does not necessarily indicate that it is the basis for loss of consciousness in that nitrous oxide, which produced quiescence, did not suppress but enhanced release. The decrease in ACh release caused by CNS depressant anaesthetics gives an experimental basis for the physostigmine-induced arousal from the prolonged aftersleep following anaesthesia in the clinical setting. Moreover, the time course of changes in ACh release during exposure to nitrous oxide implicates involvement of cholinergic neurones projecting to the cerebral cortex in the development of tolerance.

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REVIEW ARTICLE

Myocardial stunning in the neonate

P. D. Booker

Prolonged but reversible post-ischaemic ventricular dysfunction was first termed "myocardial stunning" in 1982 by Braunwald and Kloner.[16] This condition typically occurs after cardiac surgery where the heart has sustained ischaemic–reperfusion damage during operation. Neonates are not immune from such problems and as early primary repair, rather than palliation, of congenital heart lesions is now commonplace, prevention and treatment of myocardial stunning is increasing in importance to the paediatric cardiac anaesthetist. It was thought previously that myocardial stunning occurred only after ischaemia–reperfusion, but it is now apparent that stunning can also be caused by hypoxia–reoxygenation. Moreover, irrespective of the aetiology, the nature and consequences of myocyte injury may be modified by postnatal age. Experimental studies indicate that the immature heart exhibits greater functional recovery than the adult heart after a short period of ischaemia (fig. 1).[52 90] Conversely, experimental models of normothermic ischaemia without reperfusion have shown that newborn hearts develop ischaemic contracture earlier than adult hearts.[91] However, if reperfusion is started before the onset of contracture, newborn hearts are able to recover ventricular function and high-energy stores faster than adult hearts.[41 91] Thus the explanation for this apparent paradox is not solely related to experimental differences in duration of ischaemia time or use of different experimental end-points. Moreover, the response to ischaemia–reperfusion is significantly different between not only the newborn and the older neonate, but also between species,[1] which makes study comparisons and interpretation difficult. Compared with adults requiring cardiac surgery for acquired lesions, operative management differs for hypoxic neonates in that it is initiation of cardiopulmonary bypass (CPB), rather than reversal of ischaemia, which may provide the first stimulus for myocyte injury. Myocardial stunning can develop in the absence of previous ischaemia and cyanotic neonates are at particular risk of "reoxygenation injury" and subsequent myocardial dysfunction when CPB[17] or extracorporeal membrane oxygenation (ECMO)[42] is initiated. Experimental studies have shown that hypoxia–reoxygenation may be more injurious than a similar period of ischaemia–reperfusion,[47 93] although the hypoxic heart may have a greater tolerance of ischaemia than the normally oxygenated heart.[9] Myocardial stunning is caused by myocyte dysfunction. Generation of free radicals, resulting in damage to cellular proteins and phospholipids, and disruption of intracellular calcium homeostasis, are the two, non-mutually exclusive mechanisms responsible for this post-injury dysfunction.[33] Subsequently, disturbances in energy production or energy use, or both, by the contractile elements can be demonstrated. However, not only does the normal functioning of the immature myocyte differ from that of the adult, but the mechanism of the cellular response to injury is also different. The first part of this review examines the major physiological differences between myocytes from immature and adult hearts, and how those differences may affect the response to reversible injury. These age-related differences also dictate that the methods we use to prevent stunning, the subject of the second half of this review, may need to vary from those used in the adult.

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Keywords: anaesthesia, paediatric; complications, myocardial stunning; surgery, cardiovascular

Part 1. Developmental changes in cellular response to ischaemia–reperfusion or hypoxia–reoxygenation

DEVELOPMENTAL CHANGES IN SARCOLEMMAL IONIC FLUXES AND RESPONSE TO INJURY

Fluctuations in intracellular calcium ion (Ca^{++}) concentration necessary for excitation–contraction coupling are mediated by both the actions of channels in the sarcolemma and sarcoplasmic reticulum (SR). In the adult rabbit, the SR provides 90% of the Ca^{++} used to activate myofilaments.[111] The influx of Ca^{++} through voltage-dependent L-type calcium channels in the sarcolemma triggers the opening of SR Ca^{++} channels, inducing the release of large amounts of Ca^{++} from the SR.[110] In contrast, many studies using various immature mammalian heart preparations have shown that trans-sarcolemmal Ca^{++} flux is much more important than SR Ca^{++} release for the action potential-induced increases in cytosolic Ca^{++} concentration.[7 69 111] However, human neonates may have relatively mature myocytes and SR Ca^{++} release, triggered by sarcolemmal Ca^{++} flux, may assume greater significance in early postnatal life in humans than in most newborn animals.[37] Nevertheless, the smaller density of calcium current in human neonates and young children compared with adults suggests that the density of L-type calcium channels increases with postnatal age.[37] Furthermore, the rate of increase of intracellular Ca^{++} concentration,

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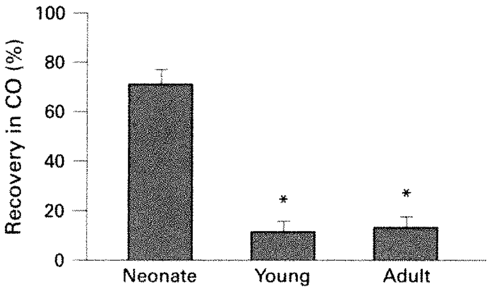

Figure 1 Isolated heart preparations obtained from rabbits aged 7–10 days (neonate), 30–40 days (young) and 6–12 months (adult) were subjected to 60 min of ischaemia at 34°C. Measurements of cardiac output (CO) obtained after 60 min of reperfusion were expressed as percentage recovery compared with pre-ischaemic values. Mean (SEM) values for the young and adult groups were significantly different from the mean neonatal value ($*P < 0.05$). Data from Pridjian and colleagues.[90]

relative to the maximum Ca^{++} concentration obtained after sarcolemmal depolarization, was found to be significantly smaller in neonates than in older children,[37] suggesting relatively low functional efficiency of SR Ca^{++} release. In immature heart preparations, much of the Ca^{++} influx through the sarcolemma is via the sodium–calcium (Na^+–Ca^{++}) exchanger, rather than L-type calcium channels (fig. 2).[7 111] The Na^+–Ca^{++} exchanger allows exchange of three Na^+ ions for each Ca^{++} ion, the relative amount of Ca^{++} removal depending on intracellular Na^+ and H^+ ion concentrations. The adenosine triphosphate (ATP)-dependent sodium pump maintains the Na^+ concentration gradient across the sarcolemma.[69] The density of Na^+–Ca^{++} exchangers in the sarcolemma of newborn mammals is species dependent, but is usually,[6 11] although not always,[7] higher than in adults. This relative abundance of Na^+–Ca^{++} exchangers correlates with the greater importance not only of this method of Ca^{++} influx during systole, but also of Ca^{++} efflux during diastole.[11 111] Factors favouring Ca^{++} influx via Na^+–Ca^{++} exchangers include prolonged sarcolemmal depolarization, decreased extracellular and increased intracellular Na^+ concentration.[111] Thus Na^+–Ca^{++} exchange may play an important role in determining Ca^{++} influx not only during cellular acidosis and ischaemia, but also during hyperkalaemic cardioplegic arrest.[25] Sarcolemmal injury, secondary to ischaemia–reperfusion, can be caused not only by free radicals but also by intracellular ATP depletion, either by its effect on channel protein function or phospholipid topology, or both.[89] Subsequent excessive inward Na^+ flux through various sarcolemmal transport pathways, including the sodium fast channels, calcium channels and the Na^+–K^+ pump, may result in intracellular Na^+ accumulation.[105] This increase in intracellular Na^+ concentration can lead to increased sarcolemmal Ca^{++} influx during ischaemia and reperfusion, secondary to Na^+–Ca^{++} exchange. Na^+–Ca^{++} exchanger activity during ischaemia–reperfusion may be greater in newborns than in adults.[73] Although acidosis partially inhibits the Na^+–Ca^{++} exchanger,[29] intracellular accumulation of Ca^{++} progressively increases if ischaemia is sustained. Experimental studies have indicated that ischaemia–reperfusion or acidosis, or both, inhibit Na^+–K^+-ATPase activity less in the newborn than in the adult.[73] However, the beneficial decrease in intracellular Na^+ and Ca^{++} accumulation this could produce is somewhat negated by a reduced basal level of activity of this enzyme in newborns.[73] Although sarcolemmal channel activity during ischaemia–reperfusion may be greater in the newborn than in the adult, both Ca^{++} influx into the cell and resting intracellular Ca^{++} concentration are determined largely by the H^+ gradient across the sarcolemma. This is because another important source of Na^+ influx is the Na^+–H^+ exchanger, particularly when there is severe intracellular acidosis induced by prolonged ischaemia–reperfusion.[116] Inhibition of Na^+–H^+ exchange is protective against ischaemia–reperfusion injury, when the H^+ ion gradient across the sarcolemma is exacerbated; it inhibits the restoration of intracellular pH and hence the Ca^{++} overload mediated by Na^+–Ca^{++} exchange.[31 38 116] Although extracellular acidosis partially inhibits the Na^+–H^+ exchanger, intracellular retention of Ca^{++} increases progressively during sustained ischaemia because this Na^+–H^+ exchange inhibition is over-ridden by the increasing intracellular acidosis.[19] Experimental studies indicate that H^+ ion extrusion from the cytosol via various sarcolemmal channels may be more efficient in the newborn than in the adult.[72 84] The ATP-dependent Ca pump in the sarcolemma does not normally transport significant amounts of Ca^{++} back out of the cell in either immature or adult hearts. Reactive oxygen intermediates, such as superoxide anion (O_2^-), may mediate both reperfusion and reoxygenation injury.[93] Hypoxia and ischaemia deplete tissue concentrations of endogenous antioxidants, increasing vulnerability to reperfusion or reoxygenation injury, or both. Reoxygenation itself

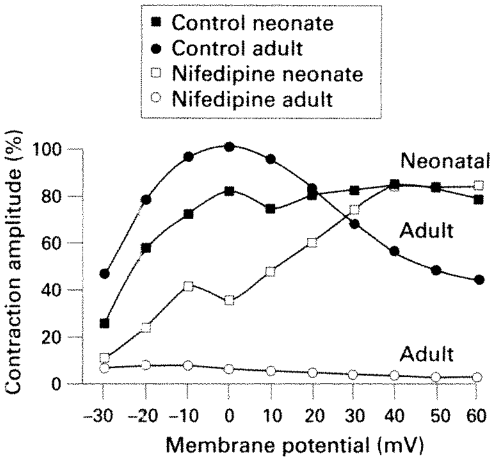

Figure 2 Isolated neonatal and adult rabbit myocytes were subjected to a series of depolarizations from a holding potential of −80 mV to various test potentials at 10-s intervals. Contraction amplitude was quantified as the maximum difference between the cell edge position before and after depolarization and expressed as mean (SEM) percentage of the normalized maximum value for each cell. The maximum contractions obtained under control conditions from neonatal myocytes were obtained at nearly all the positive membrane potentials tested, whereas myocytes from adults showed peak contraction at 0 mV with smaller depolarizations at positive membrane potentials. Exposing myocytes from neonatal rabbits to the calcium channel blocker, nifedipine, resulted in some inhibition of contractions at membrane potentials from −10 to +10 mV, but had no effect on the maximum contraction amplitude. In contrast, adult myocyte contraction was almost completely inhibited by nifedipine. At the concentration of nifedipine used (5 µmol $litre^{-1}$), Ca^{++} influx via L-type calcium channels was blocked but Na^+–Ca^{++} exchangers were unaffected. Adapted from Wetzel, Chen and Klitzner,[111] with permission.

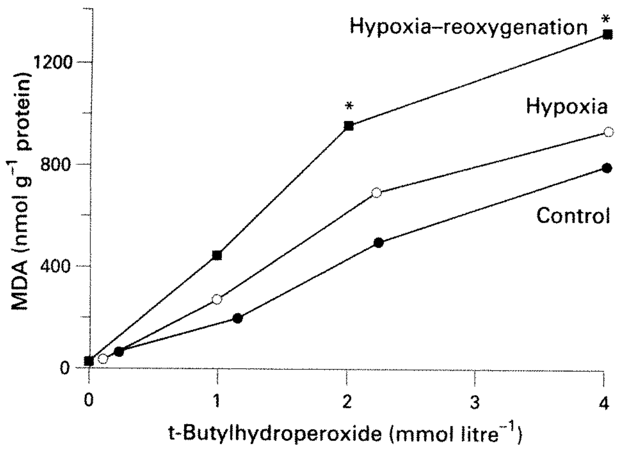

Figure 3 Left ventricular subendocardial muscle obtained from neonatal piglets before hypoxia (control), at the end of 2 h of ventilator-induced hypoxaemia and after 30 min of hypoxaemia and 60 min of reoxygenation induced during cardiopulmonary bypass was homogenized and incubated with different concentrations of the oxidant t-butylhydroperoxide. Lipid peroxidation was determined spectrophotometrically and expressed as nanomoles of malondialdehyde (MDA) per gram of protein. Lipid peroxidation after hypoxia–reoxygenation was significantly increased compared with control values at the higher concentrations of oxidant (*$P < 0.05$). Adapted from Ihnken and colleagues,[45] with permission.

may cause a further reduction in antioxidants (fig. 3). There appears to be a close correlation between antioxidant depletion, oxidant damage and cardiac dysfunction, explaining why pretreatment with antioxidants increases tolerance to reperfusion and reoxygenation injury.[77] The immature heart may be more vulnerable than the adult heart to the toxic effects of oxygen free radicals because of lower baseline concentrations of antioxidants.[85] This hypothesis is in accord with the finding that membrane damage from lipid peroxidation occurs mostly in the sarcolemmal membrane, with sarcoplasmic reticulum and mitochondrial membranes being affected to a much smaller extent.[92] Furthermore, after reperfusion injury, the newborn heart may generate more oxygen free radicals than a more mature heart.[27] The myocytes in newborns have a reduced turnover of membrane phospholipids that prevents the restoration of intact membranes from the phospholipid degradation induced by ATP depletion or free radical attack during reperfusion–reoxygenation.[105]

DEVELOPMENTAL CHANGES IN SR FUNCTION AND RESPONSE TO INJURY

In the adult, intracellular Ca^{++} concentration in the myocyte is restored to resting levels mainly as a result of SR Ca^{++}-ATPase, which binds Ca^{++} and ATP on its cytoplasmic side and translocates the cation into the SR lumen. The relative contributions of the SR pump and the Na^{+}–Ca^{++} exchanger in removing Ca^{++} from the cytosol during diastole varies among species,[69 98] but immature mammal[34] and human[37] myocytes consistently show reduced SR Ca^{++} pump activity compared with those from adult hearts. The age-related changes in myocardial relaxation and in the relaxation response to various stimuli probably relate to these limitations in SR Ca^{++} pump activity or low level of phospholamban activity, or both. None the less, the SR probably makes a significant physiological contribution to intracellular Ca^{++} flux, even in newborns. Experimental studies have produced conflicting results as to whether or not the SR in the stunned myocardium can actively take up normal amounts of Ca^{++}.[60 62] Methodological differences may account for these disparities as the capacity of SR to actively transport Ca^{++} decreases time-dependently during ischaemia.[79] However, although Ca^{++} leakage from the SR into the cytosol may occur subsequent to ischaemia–reperfusion injury in myocytes from both adult and immature hearts, excessive Ca^{++} flux across the sarcolemma is probably the predominant cause of intracellular Ca^{++} accumulation. Demonstration of a beneficial protective effect afforded by the addition of sarcolemmal calcium channel antagonists to cardioplegic solutions offers indirect confirmation of this hypothesis.[5]

DEVELOPMENTAL CHANGES IN CA^{++} UPTAKE BY THE MITOCHONDRIA AND RESPONSE TO INJURY

In the heart, mitochondria not only synthesize ATP but are involved also in the maintenance of intracellular Ca^{++} homeostasis during pathological states. The H^{+} ion electrochemical gradient that is generated by electron transport along the inner mitochondrial membrane is necessary for both processes. Furthermore, the mitochondria can be an important source of free radicals, as their electron transport train is reduced during ischaemia–reperfusion or hypoxia–reoxygenation, allowing increased leakage of electrons that can react with molecular oxygen.[33] In the adult heart, mitochondrial uptake of Ca^{++} is usually insignificant under aerobic physiological conditions, but increase in cytosolic Ca^{++} concentration in the reperfusion-injured cell leads to increased mitochondrial Ca^{++} uptake and alterations in the permeability of the inner mitochondrial membrane, resulting in swelling. Furthermore, this active Ca^{++} transport across the mitochondrial membrane inhibits utilization of the H^{+} electrochemical gradient for ATP production.[33] Mitochondria in the newborn rabbit heart show enhanced Ca^{++} uptake compared with that observed in older rabbits, even at physiological intracellular concentrations of Ca^{++}. During early neonatal life, Ca^{++} uptake by the mitochondria and phosphorylating respiratory activity decline towards adult values.[114]

DEVELOPMENTAL CHANGES IN ENERGY SUBSTRATE UTILIZATION AND RESPONSE TO INJURY

Newborn mammalian myocardium consists of small myocytes containing small mitochondria that exhibit well-coupled oxidative phosphorylation and phosphorylating respiratory activity equal to that in adults. Normally, the substrate preference of the adult heart is determined by the relative concentrations of substrates in the blood. Thus when carbohydrate concentrations are high, carbohydrate oxidation is the main energy source but, in the fasted state, the myocardium relies primarily on β-oxidation of free fatty acids.[63] In contrast, most of the energy requirements of the newborn heart are obtained from lactate oxidation and glycolysis. Experimental animal work suggests that the capacity to oxidize fatty acids and glucose is impaired in early postnatal life. However, over the first few days of life there is rapid maturation of the enzyme pathways involved in fatty acid oxidation, although glucose oxidation appears to mature at a slower rate.[65 66] The stores of myocardial glycogen in the newborn decrease soon after birth, but the ability to metabolize amino acids anaerobically is retained throughout the neonatal period; both metabolic pathways may contribute to the neonate's tolerance of hypoxia and ischaemic injury.[51] However, experimental studies have been unable to demonstrate a consistent correlation between functional recovery and tissue ATP concentration.[52 82] Furthermore, as contractile dysfunction can persist in the presence of near-normal ATP concentrations and normal mitochondrial function,[35] it would appear that energy supply is not the limiting factor preventing return of normal myocardial contractility after ischaemia–reperfusion injury. Lactate production is enhanced in immature hearts compared with adult hearts during ischaemia, but it is not known if H^+ ion production is also influenced by age. Although both anaerobic glycolysis and glycogen metabolism have lactate anions as end products, the relevant chemical reactions do not produce a net gain in H^+ ions.[28] During oxidative phosphorylation, most of the H^+ ions produced by ATP hydrolysis are used in its re-synthesis. However, when ATP is formed by glycolysis rather than by mitochondrial metabolism or creatine phosphate breakdown, H^+ ions arising from its hydrolysis are not consumed. Thus metabolic generation of protons during relatively short periods of ischaemia–reperfusion in both adult and immature hearts is primarily a result of the increased reliance on glycolysis for ATP re-synthesis. During prolonged ischaemia, however, H^+ production secondary to nucleotide degradation becomes increasingly important and is subject to developmental influences (see below). Moreover, in adults there may be some additional contribution in H^+ production related to lipolysis, membrane phosphoglyceride degradation, or both.[28] Histidine residues provide some intracellular buffering of H^+ ions, but the predominant intracellular buffer is inorganic phosphate, formed after transfer of phosphate from creatine phosphate to ADP. Unbuffered protons can leave the cell via the sarcolemmal Na^+–H^+ exchanger but interstitial proton accumulation decreases the trans-sarcolemmal H^+ ion gradient and results in a decrease in H^+, lactate ion efflux and Na^+–H^+ exchange across the sarcolemma. While tissue remains ischaemic, however, a low pH may be of benefit as it depresses SR and myofibrillar ATPase activity and thereby slows the rate of ATP use.[58] The rate of H^+ ion removal from ischaemic tissue is determined by washout. Reperfusion of ischaemic tissue, for example by cardioplegia, leads to rapid efflux of accumulated intracellular protons, resulting in secondary influx of Ca^{++} via the Na^+–Ca^{++} exchanger. Contractile failure early during ischaemia is caused by a decrease in the sensitivity of the myofilaments to Ca^{++}, together with reduced Ca^{++} flux secondary to sarcolemmal and SR calcium channel dysfunction. The decrease in myofilament sensitivity and calcium channel inhibition are caused by an increase in the intracellular concentration of inorganic phosphate and by a decrease in intracellular pH.[20 58] However, inhibition of contractile function induced by acidosis is reduced in neonates, compared with adults (fig. 4). This is because of developmental changes in SR function,[58] sarcolemmal channel activity[20] and troponin isoforms affecting the thin filament regulatory complex.[10]

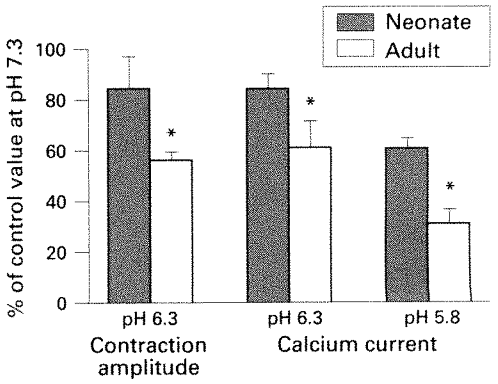

Figure 4 Effect of reducing extracellular pH on cell contraction amplitude an calcium current in isolated neonatal and adult rabbit myocytes. Results are expressed as mean (SEM) percentage (%) of control values taken at an initial pH of 7.3. All adult values were significantly different from neonatal values ($^*P<0.05$). Adapted from Chen and colleagues,[20] with permission.

DEVELOPMENTAL CHANGES IN NUCLEOTIDE SALVAGE AFTER INJURY IN THE ISCHAEMIC MYOCARDIUM

ATP is dephosphorylated to adenosine diphosphate (ADP), adenosine monophosphate (AMP) and inosine monophosphate (IMP). These precursors are unable to diffuse out of the cell and can be re-phosphorylated by viable myocytes during reperfusion to regenerate ATP. However, AMP and IMP nucleotides may be dephosphorylated to their respective precursors, adenosine and inosine, by the enzyme 5'-nucleotidase. Adenosine may either diffuse across the sarcolemma to the extracellular space or be deaminated to inosine by adenosine deaminase. Inosine may diffuse out of the cell to undergo degradation to hypoxanthine and xanthine where, as substrates for endothelial xanthine oxidase, then can form oxygen free radicals.[33] Adenine nucleotides can be restored either by relatively slow *de novo* synthesis or by faster nucleotide salvage. Reperfusion cannot replace intracellular AMP, ADP and ATP, as they are unable to be transported across the sarcolemma. The re-phosphorylation of adenosine to AMP is catalysed by the enzyme adenosine kinase, which may have a higher activity in neonates than in adults.[26] However, this nucleotide salvage pathway is possible only if adenosine is available as a precursor. Thus inadequate repletion of ATP after ischaemia–reperfusion may be caused as much by the unavailability of intracellular adenosine as by the inability of the mitochondria to phosphorylate precursors of ATP. Although reperfusion can be used to replenish intracellular adenosine, this precursor is actively transported across the sarcolemma relatively slowly and passive diffusion requires a high concentration gradient. Tissue ATP concentration and functional recovery can be enhanced after ischaemia–reperfusion if adenosine is added to cardioplegic solutions in high concentrations or endogenous adenosine concentrations are increased by inhibiting adenosine deaminase.[14] None the less, in adult rabbits, inhibition of 5'-nucleotidase preserves ATP after ischaemia–reperfusion, suggesting that nucleotide

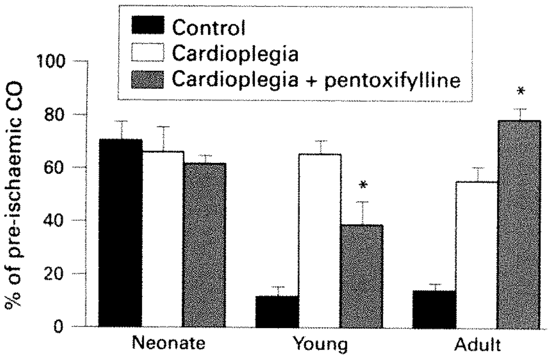

Figure 5 Isolated heart preparations from 7–10-day-old (neonate), 30–40-day-old (young) and 6–12-month-old (adult) rabbits were subjected to 60 min of ischaemia at 34°C. Control hearts from each age group received no protection, while others received either multi-dose St Thomas's Hospital cardioplegia or multidose St Thomas's Hospital cardioplegia with pentoxifylline, a 5'-nucleotidase inhibitor. Measurements of cardiac output (CO) obtained after 40 min of reperfusion are expressed as mean (SEM) percentage of pre-ischaemic values. In young and adult rabbits the values for the pentoxifylline group were significantly different from those in the cardioplegia only group ($*P < 0.05$). Data from Pridjian and colleagues.[90]

breakdown by 5'-nucleotidase may be an important mechanism of high-energy phosphate loss.[15 90] However, giving a 5'-nucleotidase inhibitor to neonatal rabbits does not improve either myocardial ATP concentrations or ventricular function after ischaemia–reperfusion (fig. 5). This is to be expected, as experimental[36] and clinical studies[64] suggest that immature hearts normally have decreased concentrations of 5'-nucleotidase compared with adult hearts. Deficiency of 5'-nucleotidase should ameliorate the loss of intracellular adenine nucleotides during reperfusion, so facilitating recovery after reperfusion by preserving the high-energy precursors able consequently to participate in salvage re-synthesis of ATP. Experimentally, 5'-nucleotidase activity may be related inversely to functional recovery after ischaemia–reperfusion,[36] but this has not been confirmed in humans.[64] This may be because of degradation of high-energy phosphates by alternative biosynthetic pathways not involving 5'-nucleotidase.

DEVELOPMENTAL CHANGES IN CONTRACTILE PROTEINS AND RESPONSE TO INJURY

Clinical studies have demonstrated significant postnatal increases in myocardial contractility.[2 23] This is related to an increase in the relative amount of contractile protein and delivery of Ca^{++} to the myofilaments. In addition, there are differences in kinase, myosin, actin and tropomyosin isoforms between the newborn and adult human, although the functional significance of this developmental change is unknown.[81] There do not appear to be any developmental variations in C-protein in the heart. However, developmental changes in troponin isoforms have been shown to be of functional importance. There are two troponin I isoforms, the relative proportion of the immature skeletal isoform decreasing with maturation. The switch to the adult cardiac isoform appears to be complete postnatally in humans.[81] There is considerable functional difference in the two troponin I isoforms such that the myofibrillar ATPase of the fetus and newborn has an increased sensitivity to Ca^{++} and desensitivity to acidosis.[10] In addition, expression of the four different troponin T isoforms differs with age, another reason why newborn myofibrils have enhanced Ca^{++} sensitivity compared with adults. Although some experimental work suggests that the decrease in contractile force in stunned myocardium is a result of a decrease in maximum calcium-activated force without desensitization of the myofilaments to Ca^{++},[39] other studies have demonstrated the converse.[74 101] It is probable that both mechanisms are involved to a greater or lesser degree. The reduction in sensitivity for Ca^{++}, secondary to myofilament injury occurring during reperfusion–reoxygenation, is probably a result of a reduced affinity of troponin C for Ca^{++}. This suggests that age-related changes may not affect the reduced affinity of troponin C for Ca^{++} induced by stunning, as troponin C is invariant throughout development. However, the altered Ca^{++} binding of troponin C may either be a direct result of reperfusion–reoxygenation injury or an indirect result of degradation of other regulatory thin filament proteins, such as troponin I and T.[74] The latter possibility increases potential developmental influences. The time course of recovery suggests that normal function returns only when irreversibly damaged protein is replaced. This hypothesis is consistent with observations that inotropic drugs that increase cytosolic Ca^{++} concentration during systole can enhance function in stunned myocardium to near normal levels.[32] The finding that maximal tension-generating capabilities of isolated myocytes can be unchanged while injured suggests that stunning has no significant effects on myosin, actin or crossbridge states.

DEVELOPMENTAL CHANGES IN CORONARY ENDOTHELIAL FUNCTION AND RESPONSE TO INJURY

Impairment of coronary vascular endothelial function induced by ischaemia–reperfusion is characterized by a reduced vasodilator response to endothelial stimulation of nitric oxide. Although hypothermia impairs release of nitric oxide from coronary endothelium, this appears to be a rapidly reversible phenomenon on rewarming.[30] Experimental work has suggested that immature hearts have better recovery of endothelial function compared with adult hearts after hypothermic ischaemia–reperfusion (fig. 6). Ischaemic hearts reperfused with leucocyte-depleted blood[95] or given monoclonal antibodies to leucocyte adhesion molecules[40] demonstrate significantly reduced endothelial reperfusion injury, suggesting that neutrophil activation is involved. Coronary vascular endothelial cells differ from myocytes in that their response to ischaemia–reperfusion is in complete contrast with their response to hypoxia–reoxygenation. The addition of a nitric oxide donor[83] or L-arginine[94] to cardioplegia, or post-CPB administration of nitroglycerin[56] have been shown to ameliorate reperfusion injury induced by coronary endothelial dysfunction. This is because during ischaemia, blood flow is stagnant and neutrophils become adherent and then "activated" during reperfusion. Nitric oxide inhibits neutrophil adherence to vascular endothelium and inhibits subsequent activation and oxygen free radical generation. Conversely, nitric oxide may accelerate reoxygenation damage when blood flow is high and neutrophil adherence unlikely.

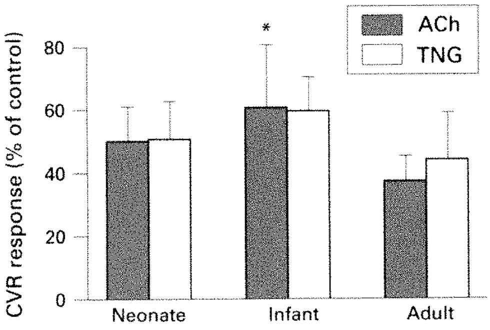

Figure 6 Isolated, blood perfused hearts from 2–7-day-old (neonate), 1-month-old (infant) and 1-yr-old (adult) sheep were subjected to 2 h of ischaemia at 15°C and given crystalloid cardioplegia every hour. Endothelial function was assessed by coronary vascular resistance (CVR) responses to the endothelium-dependent vasodilator acetylcholine (ACh) and the endothelium-independent vasodilator trinitroglycerin (TNG) and expressed as mean (SD) percentage of baseline values obtained before hypothermia. The ACh value for the infant group was significantly different from that of the adult group ($*P < 0.05$). Data from Hiramatsu and colleagues.[41]

Constitutive nitric oxide synthase activity is related to oxygen tension, and uncontrolled reoxygenation using a high arterial partial pressure of oxygen leads to excessive nitric oxide production. This excess of nitric oxide reacts with superoxide anion to generate highly toxic reactive oxygen intermediates that can cause lipid peroxidation and subsequent myocardial dysfunction. Experimental studies have shown that suppression of nitric oxide production during controlled reoxygenation can reduce endothelial and myocardial dysfunction.[46]

Part 2. Principles of prevention of myocardial stunning in the neonate

Determination of the optimal method of myocardial protection in the neonate has been the subject of much experimental research. However, the use of diverse mammalian species, each with different rates of development, may appear an unreliable basis to provide appropriate data. Moreover, many studies have relied on isolated heart preparations that fail to model non-coronary collateral flow, neurohormonal influences and the effects of cardiopulmonary bypass (CPB). Nevertheless, this experimental evidence, together with accumulating clinical experience, has provided useful guiding principles that are helping clinicians find safe, effective methods of enhancing myocardial protection for the neonate at risk of stunning. Most techniques of intraoperative myocardial protection rely on reducing myocardial oxygen demand which is determined primarily by electromechanical activity and secondarily by metabolic rate. Electromechanical work is minimized by potassium-induced diastolic arrest, and basal metabolic rate is reduced with hypothermia. However, the effects of hypothermia and cardioplegic arrest on myocardial oxygen consumption may differ in the neonate compared with the adult, and it would appear that for neonates, cardioplegic arrest may add little extra myocardial protection to that offered by hypothermia alone (fig. 7).[44 49 54 55] Thus profound hypothermic circulatory arrest, without the use of cardioplegia, remains a widely used method of combining myocardial protection with a bloodless and motionless surgical field. Non-neurological complications and haemodynamic profile are similar if low-flow CPB or circulatory arrest is used.[109] However, the higher incidence of neurological complications associated with circulatory arrest[12] has revived interest in strategies that allow perfusion to be maintained throughout surgery in even the smallest neonate. This has led to the development of specific cardioplegic techniques for neonates. In addition to the main preventative strategies of hypothermia and cardioplegia, other adjuvant techniques are under investigation.

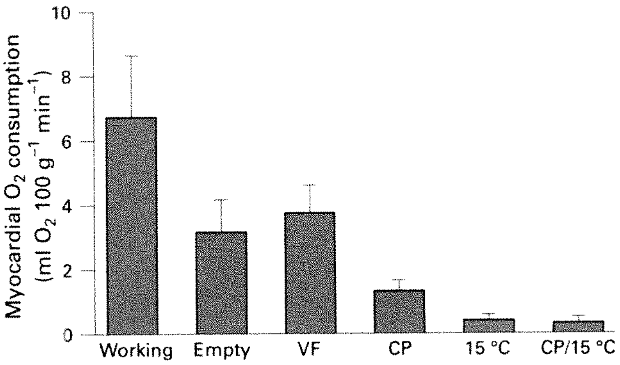

Figure 7 Mean (SD) myocardial oxygen (O_2) consumption (expressed in millilitre of O_2 per 100 g of ventricular tissue per minute) was measured in isolated neonatal piglet heart preparations when working, empty beating, fibrillating (VF), cardioplegic arrested at normothermia (CP), hypothermic (15°C) or cardioplegic arrested at 15°C. All values were significantly different except those obtained at 15°C ($P < 0.05$). Data from Jessen, Abd-Elfattah and Wechsler.[49]

HYPOTHERMIA

Myocardial temperature may be decreased using perfusion cooling or topical cooling, or both. Topical cooling can be achieved by bathing the heart surface with ice slush, although this method is ineffective at cooling the most vulnerable sub-endocardial regions and most paediatric cardiac surgeons use topical cooling only as an adjunct to perfusion-induced cooling. Cold cardioplegic solutions or CPB, or both, are very effective at cooling the heart and can be used in combination. It is comparatively easy in neonates to ensure that CPB-induced hypothermia produces temperature equilibration throughout all tissues of the body, as neonates have a higher proportion of vessel-rich tissues than adults. Whole body perfusion cooling allows low CPB flow rates or circulatory arrest, as tissue energy requirements are substantially reduced at low temperature. However, the temperature dependency of biochemical reactions is variable and hypothermia, therefore, can lead to derangement of intracellular homeostasis. In particular, the variable effect of low temperature on sarcolemmal[102] and SR[61] channels results in increased intracellular Ca^{++} concentration. Thus although hypothermia is believed to improve tolerance to ischaemia, intracellular Ca^{++} accumulation induced by hypothermia may lead to exacerbation of ischaemia–reperfusion injury. Experimental studies have indicated that hypothermic perfusion before ischaemia may attenuate functional recovery after reperfusion, but that this detrimental effect can be ameliorated by hypocalcaemic perfusion before[5] or during cardioplegic arrest.[13] One clinical study suggested that rapid myocardial cooling could result in significant damage and recommended "slow" cooling before induction of cardioplegic arrest.[112] However, more recent experimental studies have been unable to confirm that rapid cooling is more detrimental than slow cooling to the immature myocardium.[54,55] Furthermore, prolonged hypothermic CPB perfusion may itself be deleterious to the immature heart,[44,100] particularly if electromechanical activity is sustained.[107] In addition to intracellular Ca^{++} accumulation, prolonged hypothermic perfusion may be associated with hyperglycaemia and inhibition of mitochondrial function, which leads to metabolic derangement and decreased ATP production.[107] In clinical practice, perfusion cooling at a rate of 1°C min^{-1} is used as a compromise between restricting the duration of pre-arrest hypothermic perfusion and optimizing tissue temperature equilibration. Inter-species differences and use of different study end-points have complicated the identification of the optimal temperature for prolonged myocardial protection. A study of ATP metabolism and contractility in canine hearts subjected to either normothermic (37°C) or hypothermic (15°C) cardioplegic arrest found similar reductions in tissue ATP concentrations in each group.[99] However, hypothermic perfusion resulted in a threefold increase in adenosine and AMP concentrations compared with normothermic hearts, suggesting that hypothermia to 15°C may produce beneficial inhibition of nucleotide breakdown. Furthermore, myocardial function was not significantly different between the two groups, suggesting that hypothermia to 15 °C is not detrimental to myocardial function. It must be emphasized, however, that these relatively innocuous effects of hypothermia relate to arrested hearts; when electromechanical activity is maintained, hypothermic perfusion may cause myocardial injury.[107] In rabbits, there appears to be a biphasic relationship between the extent of protection and degree of hypothermia (fig. 8). Decreasing myocardial temperatures to less than approximately 20°C did not confer additional protection, but higher temperatures provoked rapid loss in protection.[57] In contrast, a study involving neonatal pigs found that time to ischaemic contracture and decline in ATP concentrations were significantly less in hearts maintained at 12°C compared with hearts at 19°C. Moreover, the protective effects of hypothermia were significantly reduced if pre-ischaemic ATP concentrations were low.[113] One clinical study has suggested that myocardial temperatures less than approximately 15°C may inhibit energy substrate production by anaerobic glycolysis to a greater degree than energy consumption.[53] In keeping with these findings, most centres using circulatory arrest techniques aim to maintain myocardial temperatures between 15 and 20°C throughout surgery. The period immediately after corrective surgery is undoubtedly crucial to ultimate recovery, as reperfusion–reoxygenation injury may be occurring at the same time as oxygen consumption is increasing, secondary to the increase in metabolic rate and initiation of reparative and electromechanical activity. Inevitably, it has been difficult to identify the relative importance of the effects of reperfusion, reoxygenation and rewarming on the immature heart. Experimental studies have shown that hypothermia-induced depression of myocardial function and depression of metabolic activity may persist during rewarming.[106,107] Moreover, rewarming from profound hypothermia can cause structural derangement of the sarcolemma, possibly caused by lipid peroxidation.[67] The standard rewarming rate of 1°C min^{-1} is a compromise between the time required for optimizing tissue temperature equilibration and keeping reperfusion of the non-working heart to a minimum.[59] None the less, clinical experience indicates that a significant increase in contractility occurs during the later stages of rewarming. Thus some prolongation of normothermic perfusion to the *working* heart may allow better myocardial recovery before the workload of the heart increases as a result of the increase in systemic vascular resistance after CPB.

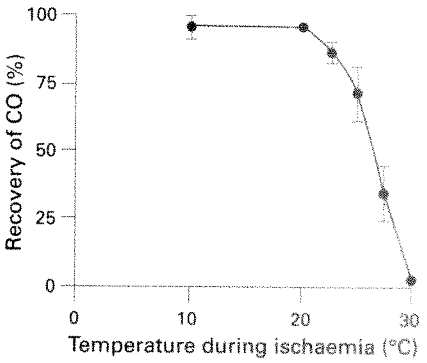

Figure 8 Isolated working heart preparations obtained from neonatal rabbits were perfused with oxygenated, buffered fluid for 20 min at 37°C before single infusion of crystalloid cardioplegia and ischaemic arrest at maintained temperatures of 10, 20.0, 22.5, 25.0, 27.5 or 30.0°C for 4 h. Cardiac output (CO) was measured after 60 min of working reperfusion and expressed as mean (SEM) percentage recovery compared with pre-ischaemia values. Data from Kempsford and Hearse.[57]

CARDIOPLEGIA

Although there is widespread use of cardioplegia in paediatric cardiac surgery, optimal temperature, composition and delivery pressure of the solution remain subjects of controversy. The main reason for using cardioplegia is to maintain the heart in diastolic arrest while the aorta is clamped and there is no coronary blood flow. In addition, the cardioplegic solution can be used to assist in the uniform cooling or warming of the arrested heart. However, if profound hypothermia is induced by CPB, the additional cooling effect of cardioplegia infusion on the myocardium may be relatively small. Moreover, experimental evidence suggests that solutions at temperatures <4°C may have detrimental effects, probably secondary to endothelial injury.[4] Clinical studies in adults suggest that use of warm cardioplegia to induce diastolic arrest or infusion again, or both, immediately before unclamping the aorta may reduce reperfusion–reoxygenation damage,[18] although this has not been confirmed in neonates. The cardioplegic solution usually contains a high concentration of K^+ (15–20 mmol $litre^{-1}$) that produces electromechanical arrest by reducing the resting membrane potential and inactivating the fast sodium channel in the sarcolemma. Return of electromechanical activity while the aorta is clamped, which increases the possibility of myocardial injury, is more likely to occur when myocardial temperatures are high or when non-coronary collateral flow results in washout of the high concentration of K^+ in the extracellular fluid. Thus in order to maintain diastolic arrest when myocardial temperature is greater than approximately 20°C, cardioplegic infusions may need to be given every 15–30 min. Experimental studies using isolated cell cultures have demonstrated age-related differences in the response of the myocyte to hyperkalaemia.[25, 71] In adults, hyperkalaemia produces a significant increase in cell volume and reduction in contractility that is not seen in myocytes from immature rabbits. This developmental difference may relate to calcium-induced myocyte injury, as hyperkalaemia-induced depolarization of immature myocytes does not result in as great an increase in intracellular Ca^{++} concentration as has been demonstrated in adults. The mechanism for this Ca^{++} influx during hyperkalaemia varies with age. In adults the primary entry route for the increase in cytosolic Ca^{++} is the sarcolemmal calcium channel, whereas in the immature myocyte it is the Na^+–Ca^{++} exchanger.[25] The SR has no influence on cytosolic Ca^{++} during hyperkalaemia at any age. The potential for hypothermia and hyperkalaemia to cause calcium influx has made the optimal Ca^{++} concentration of cardioplegia for the neonate a controversial topic.[70] Immature rabbit hearts receive maximum myocardial protection when the cardioplegic solution contains only Ca^{++} 0.3–0.4 mmol litre^{-1},[8] although neonatal piglet hearts appear to benefit from normocalcaemic solutions.[87] More recent work[13] may have helped resolve this issue. Myocardial protection appears to be independent of cardioplegic Ca^{++} concentration in normal neonatal piglet hearts. However, when a comparable group of piglets subjected to hypoxia–reoxygenation injury before cardioplegic arrest are given normocalcaemic blood cardioplegia, they demonstrated significantly reduced functional recovery and ATP concentrations after CPB compared with those given hypocalcaemic blood cardioplegia (fig. 9). In addition, the concentration of magnesium (Mg^{++}) in the cardioplegic solution has a significant influence on the extent of Ca^{++} influx induced by hyperkalaemia. Increasing concentrations of extracellular Mg^{++} can displace Ca^{++} from the glycocalyx, thus reducing the amount of extracellular Ca^{++} available for trans-sarcolemmal entry, whether by calcium channel or Na^+–Ca^{++} exchanger.[25] It follows that the optimum Ca^{++} concentration of cardioplegia for the neonate varies depending on the complex interaction between pre-injury hypoxia, duration of ischaemia, Mg^{++} concentration of the solution and myocardial temperature. Although the relative merits and demerits of blood and crystalloid cardioplegic solutions remain subjects of controversy, it appears that blood is becoming the preferred vehicle.[18] The main advantages of blood cardioplegia are its greater buffering and oxygen carrying capacities compared with crystalloid cardioplegia. Although there is a shift in the oxyhaemoglobin dissociation curve to the left secondary to hypothermia, oxygen unloading from cold blood cardioplegia is greater than that expected because of a compensating rightward shift induced by myocardial tissue acidosis, hypercapnia and rewarming.[43] The buffering capacity of blood cardioplegia is usually much greater than that of crystalloid cardioplegia because of the presence of the amino acid histidine, which has an imidazole group that can accept protons. The other potential advantages of blood cardioplegia, which include its beneficial oxygen free radical scavenging, rheological and oncotic properties, do not appear to be subject to developmental influences. The few experimental studies comparing multi-dose blood and crystalloid cardioplegic solutions in hypothermic, immature hearts have shown that the blood vehicle offers better myocardial protection.[24, 87] A single dose of crystalloid cardioplegic solution given at the onset of ischaemia may add to the protection offered by profound hypothermia,[80] but repeated doses appear to be of little further benefit or may even inhibit subsequent recovery of the immature heart.[68] This detrimental effect of multi-dose cardioplegia may be a result of the repeated alteration in H^+ ion gradient between the inside and outside of the cell, causing ions to move through the Na^+–H^+ exchanger during every infusion.[7] There has been concern that hyperkalaemic cardioplegia may induce endothelial cell injury, although high pressure delivery of the solution may be more to blame.[30] High infusion pressure can induce endothelial injury and although control of infusion pressure does not guarantee normal shear stress in the epicardial coronary artery, it is minimized at aortic root pressures of 90–120 mm Hg in the adult dog.[30] Similarly, a study using mature rats has shown that cardioplegia delivered at pressures of 75–105 mm Hg produced better functional and metabolic myocardial recovery than when cardioplegia delivery was at either higher or lower pressures (fig. 10).[48] Thus although there has been no confirmatory clinical evidence, it would seem advisable that in the human neonate, cardioplegia is infused at normal aortic root pressures, that is 60–80 mm Hg. Similarly, reducing coronary artery pressure during initial reperfusion may improve endothelial function[96] by limiting excessive nitric oxide production induced by shear stress.[46] Experimental studies have shown that amino acid enrichment of cardioplegic solutions improves both meta-

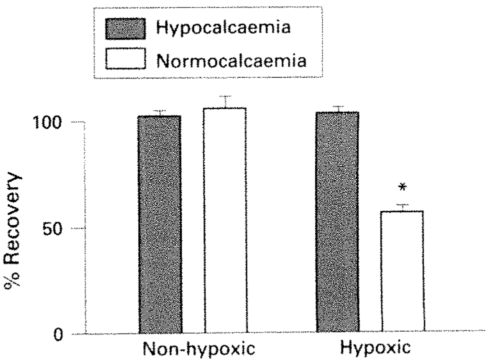

Figure 9 Neonatal piglets were placed on hyperoxaemic cardiopulmonary bypass (CPB) and subjected to either multi-dose normocalcaemic or hypocalcaemic blood cardioplegic arrest for 70 min. Half the piglets had previously undergone ventilation for 60 min with an inspired oxygen concentration of 8% to render them hypoxic. Myocardial function was assessed 30 min after CPB and expressed as mean (SEM) percentage of pre-CPB values. Both hypocalcaemic and normocalcaemic multi-dose blood cardioplegic solutions allowed complete recovery in the non-hypoxic group. In contrast, the group who had been exposed to acute hypoxia–reoxygenation injury before cardioplegic arrest demonstrated significantly reduced recovery when normocalcaemic blood cardioplegia was used ($*P < 0.05$). Adapted from Bolling and colleagues,[13] with permission.

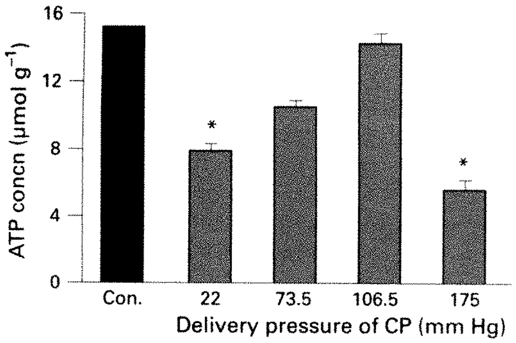

Figure 10 Isolated heart preparations from adult rats were perfused with oxygenated buffered solution before multi-dose crystalloid cardioplegic arrest for 210 min at 12°C. Adenosine triphosphate (ATP) concentration in each heart was determined after 60 min of reperfusion. Each group of hearts had cardioplegia (CP) delivered at a different pressure. Mean (SEM) ATP concentrations in hearts receiving CP at pressures of 22 and 175 mm Hg were significantly lower than pre-ischaemia control values (Con.) ($*P < 0.05$). Adapted from Irtun and Sirlie,[48] with permission.

bolic and functional recovery of ischaemic immature myocardium.[86, 108] In addition to replenishing myocyte energy substrates, glutamate and aspartate inhibit L-arginine transport and subsequent production of reactive oxygen intermediates, hence reducing reoxygenation injury.[46] Experimental studies have shown that fumarate may offer metabolic support without causing the systemic vasodilatation that characterizes glutamate administration.[86] Fumarate, a Krebs' cycle intermediate, can be reduced to succinate with the concomitant oxidation of NADH, resulting in ATP production, even under hypothermic, ischaemic or hypoxic conditions. Furthermore, in addition to its metabolic effects, fumarate stimulates mitochondrial uptake of Ca^{++} under anoxic conditions and may also act as a free radical scavenger. Other cardioplegic additives that have produced encouraging amelioration of stunning injury to the myocyte or endothelium, or both, include nitric oxide donors, L-arginine, adenosine and potassium channel blockers. It is important to differentiate between reperfusion injury and reoxygenation injury when reviewing the use of agents that affect nitric oxide production (see also DEVELOPMENTAL CHANGES IN CORONARY ENDOTHELIAL FUNCTION AND RESPONSE TO INJURY above). Reperfusion injury may be reduced by using agents that enhance nitric oxide production,[83] whereas reoxygenation injury can be reduced by using agents that suppress nitric oxide production.[46] Alternatively, reoxygenation injury can be minimized by delaying and controlling reoxygenation (see CONTROLLED REOXYGENATION below). Adenosine and ATP-sensitive potassium channel blockers inhibit hyperkalaemic-induced Ca^{++} influx into the myocyte,[50] and therefore may not be particularly beneficial in neonates. However, both adenosine and ATP-sensitive potassium channels have been implicated in the mechanism of preconditioning (see PRECONDITIONING next).

PRECONDITIONING

Repeated ischaemic episodes would be expected to have a cumulative adverse effect on myocardial function, but instead of becoming sensitized, the heart exhibits a marked resistance to myocardial injury after subsequent prolonged ischaemia. This capacity for endogenous protection, termed preconditioning, can also be initiated by other stimuli such as hypoxia.[22] When preconditioned myocardium is subjected to sustained ischaemia, ATP use and anaerobic glycolysis occur at much slower rates than normal, and the duration of ischaemia that can be tolerated before irreversible injury to the myocyte occurs is greatly extended. The mechanism for preconditioning is unknown, but must involve the release of endogenous substances from the ischaemic myocardium because regional preconditioning can protect remote non-preconditioned tissue. Current research has implicated adenosine A1 and α_1 receptors, inhibitory G proteins, ATP-sensitive potassium channels and protein kinase C in this phenomenon.[22, 97] Preconditioning requires a minimum duration of initiating insult and its protective effects last only a few hours. Early studies established that preconditioning could limit infarct size and reduce reperfusion injury-induced ventricular arrhythmias. More recently, experimental studies have demonstrated that preconditioning can enhance the recovery of stunned human myocardium[21] and animal work has demonstrated that preconditioning preserves normal mitochondrial function and facilitation of glycolysis during reperfusion.[115] Preconditioning has been demonstrated in adults undergoing coronary artery surgery,[117] although the efficacy of this phenomenon in humans remains a subject of debate.[88] More clinical studies in adults undergoing cardiac surgery are required before the therapeutic potentials for paediatric practice can be explored.

CONTROLLED REOXYGENATION

Experimental studies have demonstrated that hyperoxic reoxygenation of previously hypoxic immature piglet hearts causes oxidant injury, reduction in anti-oxidant reserve capacity and a decrease in myocardial contractility.[78] The extent of oxidant injury secondary to reoxygenation appears to correlate with nitric oxide production. Suppression of excessive nitric oxide production by controlling reoxygenation and supplementing blood cardioplegia with glutamate–aspartate increases functional recovery.[46] Experimental studies have shown that reducing oxygen tension to approximately 100 mm Hg during reoxygenation avoids oxidant injury, retains normal anti-oxidant reserve and improves myocardial functional recovery (fig. 11). These data suggest that reoxygenation injury can be minimized by initiating CPB at the ambient oxygen tension of the hypoxic neonate and delaying controlled reoxygenation until after cardioplegic arrest. Immature hearts subjected to reoxygenation injury before cardioplegic arrest have increased reperfusion injury and decreased functional recovery compared with hearts not subjected to reoxygenation before arrest, even if blood cardioplegia is used. Supplementation of the cardioplegic solution or the CPB prime with antioxidants,[77] or strategies designed to reduce nitric oxide production may reverse this increase in reperfusion injury.[46] A further increase in recovery can be produced if reoxygenation injury can be minimized by delaying reoxygenation until cardioplegic arrest is initiated.[75]

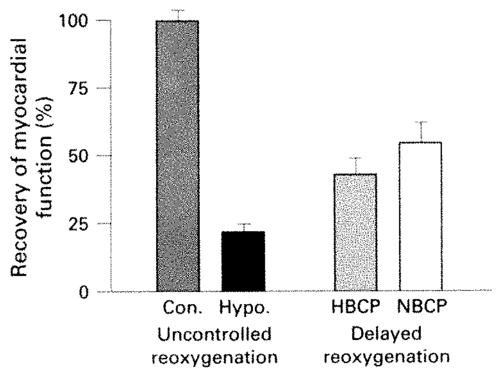

Figure 11 In immature piglets on cardiopulmonary bypass (CPB), the aorta was clamped for 30 min while given multi-dose blood cardioplegia (BCP) and reperfused for 25 min before measurements of myocardial function were obtained 30 min after CPB. The control group (Con.) were normoxaemic before being placed on hyperoxaemic (Po_2 = 53.3 kPa) CPB and given hyperoxaemic BCP (Po_2= 53.3 kPa). The other group of piglets had been made hypoxic (Hypo.) by lowering their inspired oxygen concentration to 7% for 120 min before CPB. They were then subjected to either uncontrolled reoxygenation (placed on hyperoxaemic CPB and then given hyperoxaemic BCP) or reoxygenation was delayed until the aorta was clamped and then received either hyperoxaemic (HBCP) or normoxaemic BCP (NBCP). After CPB, myocardial function was compared with pre-CPB values and expressed as mean (SEM) percentage recovery. Previously hypoxic piglets achieved their best recovery when reoxygenation was delayed until after BCP arrest and on receiving normoxaemic BCP (NBCP). Adapted from Ihnken and colleagues,[46] with permission.

OTHER ADJUVANT THERAPY

An infusion of glucose–potassium–insulin given before stunning may promote glucose uptake by the myocardium and increase intracellular energy substrate concentrations.[103] In addition, insulin reduces the concentration of free fatty acids and promotes myocardial glycogen synthesis. Moreover, Krebs' cycle carbohydrate metabolism after reperfusion is improved, as insulin stimulates the activity of pyruvate dehydrogenase, which is normally inactivated during ischaemia. Clinical studies in adults have shown that the haemodynamic effects of catecholamines may be increased by using high-dose insulin to shift myocardial metabolism from free fatty acid oxidation to carbohydrate metabolism.[104] However, the practical difficulties of maintaining normoglycaemia while giving insulin throughout the perioperative period continue to make this therapy relatively unpopular. Adults given infusions of glutamate during stunning have demonstrated improved haemodynamic performance and metabolic profile.[103] Glutamate and aspartate enhance glycolysis, improve lactate clearance, replenish Krebs' cycle intermediates and stimulate alternative anaerobic pathways for regeneration of ATP during ischaemia–reperfusion. Although these potential benefits explain why preoperative infusions of certain amino acids have been advocated, glutamate causes pronounced dose-related systemic vasodilatation, and it is usually given only as an additive to the cardioplegic solution or CPB prime.[76 103]

Conclusions

As primary corrective surgery in the neonate becomes more common, more complex and more time consuming, the search continues for therapeutic strategies that will extend the safe duration of induced myocardial ischaemia. Although the use of animal models to investigate the influence of age on myocardial stunning is understandable and necessary, it also implies that such work should be subject to cautious interpretation before extrapolation of their conclusions to the human neonate. Nevertheless, the information engendered from many of these studies has suggested modifications in our management of neonates undergoing cardiac surgery that have subsequently proved useful and efficacious. Now that specific biochemical markers of myocardial damage that can be sampled from coronary sinus outflow have been identified, clinical studies should be able to help further refine and optimize our currently available methods of myocardial protection for this challenging group of patients.

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British Journal of Anaesthesia 1998; **80**: 384–385

SHORT COMMUNICATION

Neuromuscular monitoring by intensive care nurses: comparison of acceleromyography and tactile assessment

R. Greer, N. J. N. Harper and A. J. Pearson

Summary

We have compared tactile assessment of the train-of-four (TOF) count and TOF ratio by nursing staff, with measurements made by a new acceleromyographic monitor, the TOF-Watch. We assessed neuromuscular block in 30 sedated intensive care patients receiving a continuous infusion of atracurium. Five nurses made a tactile assessment of neuromuscular block in each patient within a 5-min period. Each assessment was paired with a blinded TOF-Watch measurement. The nurses were accurate in assessing twitch count in 55% of measurements and they tended to overestimate the degree of block using tactile assessment of TOF ratio. (*Br. J. Anaesth.* 1998; **80**: 384–385)

Keywords: Intensive care; monitoring, neuromuscular function; neuromuscular block, measurement of response; equipment, acceleromyograph

The use of neuromuscular blocking drugs in the intensive care unit is commonplace. It is important to monitor neuromuscular function in the critically ill because the action of these drugs varies widely in this population.[1] Tactile assessment of the train-of-four (TOF) is used commonly in anaesthetic practice to assess the degree of block, but there are few published data on tactile assessment of neuromuscular block in the intensive care unit. The majority of routine monitoring of vital signs in the intensive care unit is performed by nurses. Our aim was to compare the accuracy of nurse assessment of TOF responses with acceleromyography, which is a reproducible method of measurement.

Acceleromyography uses the principle that acceleration of a contracting muscle is proportional to the force of contraction (Newton's second law). In a previous study it was demonstrated that a similar acceleromyography device gave results comparable with those of a standard mechanometric device (Myograph 2000) but there was greater variation in responses to acceleromyography.[2] The TOF-Watch (Organon teknika) is an electromyographic device. It comprises a standard nerve stimulator and a small piezoelectric acceleration transducer that is attached to the thumb. The TOF-Watch enumerates the TOF ratio and TOF count on a liquid crystal display.

Methods and results

We investigated 30 stable, sedated adult patients receiving an infusion of atracurium in our intensive care unit. ECG-type electrodes were placed over the ulnar nerve of both wrists. The TOF-Watch was used to obtain acceleromyographic measurements of neuromuscular block at one thumb (adductor pollicis). The stimulating leads of the TOF-Watch were then disconnected and reconnected to similar electrodes on the contralateral wrist when tactile assessment was made. In this way the same nerve stimulator was used for tactile and acceleromyographic measurements at different wrists. We used two wrists to avoid displacement of the sensitive acceleration transducer between measurements: a small change in position could have affected the results. The same stimulating current was used at both wrists (60 mA). We ensured that the electrode position was identical at both wrists and we assigned at random the dominant and non-dominant hands for measurement. The nurse caring for the patient (nurse A) made a tactile TOF assessment and then a TOF-Watch measurement. Four subsequent assessments were made by four different nurses who were blinded to the TOF-Watch result. At the same time as each tactile assessment, nurse A made a TOF-Watch measurement on the patient's other hand. Each of the four nurses stated the number of twitches she could feel in response to a TOF stimulus and if four were palpable she declared a TOF ratio. One minute elapsed between measurements. In this way we obtained five pairs of data for each patient. The nurses were given standard instructions in the simple theory and relevance of neuromuscular function; however, they were not given practical experience in the technique before commencement of the study.

The nurses estimated correctly the twitch count in 80 assessments (54%); they overestimated the count in 38 assessments (25.3%) and underestimated it in 31 (20.6%). Seventeen percent of assessments were inaccurate by two twitches (fig. 1). A Bland and Altman plot[3] demonstrated that nurses tended to overestimate the TOF ratio by a small amount. There was also greater variability among the nursing assessment of the TOF ratio than among the TOF-Watch measurements. No learning effect could be demonstrated by comparing the assessments of the first 10 patients and the last 10.

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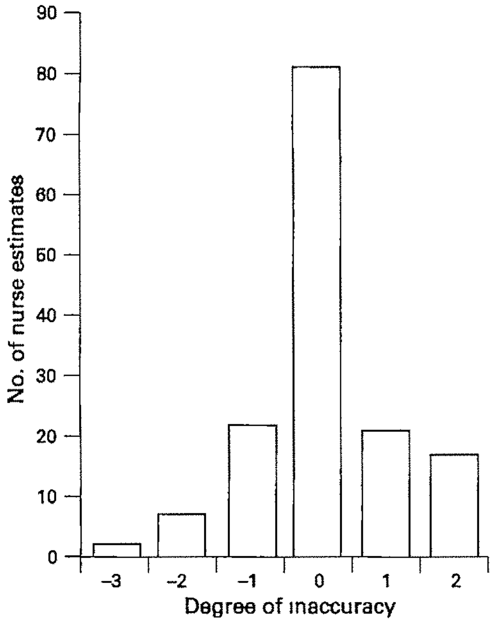

Figure 1 Degree of inaccuracy with which ICU nurses estimated the number of train-of-four responses. A degree of inaccuracy of −1, for example, indicates that the nurses were able to feel one fewer response than the number measured by the TOF-Watch.

Comment

The use of neuromuscular blocking drugs in the intensive care unit is common. However, monitoring of neuromuscular function in the intensive care unit is not performed routinely. It is important to assess the degree of block in critically ill patients because the action of these drugs varies widely in this population. Changes in the pharmacokinetics and pharmacodynamics of neuromuscular blocking drugs may occur and these patients may demonstrate increased or decreased sensitivity to these agents. Differing degrees of block are required depending on the clinical indication for the use of neuromuscular blocking agents in the intensive care unit.

Acceleromyography has been described as a method of measurement of neuromuscular block during anaesthesia.[4] Acceleromyographic and mechanomyographic measurements of TOF responses compare well during stable neuromuscular block. Our study of tactile assessment of TOF count found that the nurses were inaccurate in 45% of measurements and the degree of inaccuracy was two twitches or more in 17% of cases. Underestimation of twitch count leads to overestimation of the level of block, which may mislead doctors and nurses into reducing the rate of infusion of atracurium. A patient in whom a deep level of block is required to avoid an increase in intracranial pressure or to improve thoracic compliance may be put at risk by this course of events.

Measurement of TOF ratio is an important method of assessing recovery from neuromuscular block. It has been shown that tactile assessment of TOF ratio by medical staff is inaccurate at low levels of block.[5] Our results demonstrated that nursing staff tended to overestimate TOF ratio. There was also greater variability in the assessments by the nursing staff. Full recovery from neuromuscular block is important when it is necessary to make neurological or respiratory assessments after a period of block. Underestimation of the degree of block may lead to inaccurate patient assessment and inappropriate changes in therapy.

We suggest that acceleromyography is a useful tool in the intensive care unit. In particular, the TOF-Watch appears to be an appropriate neuromuscular monitor in this setting. The accuracy of tactile assessment of TOF twitch count and TOF ratio by nursing staff may not be a sufficient basis on which to make decisions on clinical management in the intensive care unit.

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British Journal of Anaesthesia 1998; **80**: 386–388

CASE REPORT

Accelerated recovery and disposition from rocuronium in an end-stage renal failure patient on chronic anticonvulsant therapy with sodium valproate and primidone

J. J. DRIESSEN, E. N. ROBERTSON, L. H. D. J. BOOIJ AND T. B. VREE

Summary

An end-stage renal failure patient, receiving chronic treatment with the anticonvulsants, sodium valproate and primidone, showed accelerated recovery with enhanced elimination ($T_{1/2}^{z}$ = 52 min) and clearance(Cl = 14.4 ml min^{-1} kg^{-1}) of rocuronium. The pharmacokinetic and pharmacodynamic effects of rocuronium in this patient are compared with those published for healthy and renal failure patients. Increased hepatic binding of rocuronium rather than metabolism is suggested as the possible cause of this effect. (*Br. J. Anaesth.* 1998; **80**: 386–388)

Keywords: anticonvulsants; kidney, failure; neuromuscular block, rocuronium; pharmacokinetics, rocuronium

It is well documented that patients treated chronically with anticonvulsant drugs such as phenytoin or carbamazepine are resistant to the effects of non-depolarizing neuromuscular blocking drugs.[1–5] Larger doses of neuromuscular blocking agents are required to produce a given degree of neuromuscular block and recovery from paralysis is faster. We report the case of an end-stage renal failure patient, receiving chronic treatment with the anticonvulsants, sodium valproate and primidone, who showed marked resistance to neuromuscular block, with enhanced elimination and clearance of rocuronium.

Case report

A 40-yr-old male (1.96 m, 69 kg) was undergoing placement of a peritoneal dialysis catheter. The patient suffered from end-stage renal failure caused by chronic glomerulonephritis and had been on haemodialysis for 2 yr. His daily urine output was approximately 100 ml and creatinine clearance <5 ml min^{-1}. Because of hypertension, mild left ventricular hypertrophy was present. After meningitis in early childhood, he had developed epileptic seizures. With his present medication, he had experienced no seizures since 1983. The patient had given written informed consent to participate in a study into the pharmacokinetics and pharmacodynamics of rocuronium 0.6 mg kg^{-1} in patients with renal failure, but the investigators were unaware of his antiepileptic therapy which would have excluded him from the study.

Haemodialysis was performed 24 h before surgery. Preoperative laboratory investigations included: haemoglobin 5.4 mmol litre^{-1}, serum creatinine 549 µmol litre^{-1}, serum urea 15.7 µmol litre^{-1}, serum albumin 34 g litre^{-1}, total serum protein 63 g litre^{-1}, serum ALAT/GPT 9 iu litre^{-1}, serum ASAT/GOT 15 iu litre^{-1} and potassium 4.8 mmol litre^{-1}.

His routine medication was: metoprolol 200 mg twice daily, minoxidil 10 mg twice daily, primidone 250 mg twice daily, sodium valproate 300 mg four times daily and calcium carbonate 500 mg five times daily. I.v. flucloxacillin 1 g, three times daily was given in the perioperative period as antibiotic prophylaxis.

The patient was premedicated with paracetamol 1 g and oxazepam 10 mg orally, 1 h before surgery. Before surgery, systolic arterial pressure was 150/80 mmHg with a heart rate of 72 beat min^{-1}. General anaesthesia was induced with fentanyl 0.1 mg and propofol 2 mg kg^{-1} via an i.v. infusion, and was maintained with continuous infusion of propofol 6–10 mg kg^{-1} h^{-1}, with supplementary bolus doses of fentanyl 0.1 mg as required. When the patient was asleep, neuromuscular function was monitored using transcutaneous supramaximal square wave stimuli of 0.2 ms delivered at 0.1 Hz with surface electrodes over the ulnar nerve at the wrist. Muscle contraction of the adductor pollicis was measured mechanomyographically with a Grass FT-03 force displacement transducer. After stabilization of the control twitch response for 5 min, rocuronium 42 mg (0.6 mg kg^{-1}) was administered as a fast i.v. bolus before tracheal intubation. Thereafter the patient's lungs were ventilated with 40% oxygen in nitrous oxide to achieve an end-tidal carbon dioxide partial pressure of 4–4.7 kPa. After the single twitch response recovered to 25%, train-of-four (TOF) stimuli were used every 12 s. Onset time (time to maximum twitch depression) time to recovery of the single twitch response to 25% and time to recovery of the TOF ratio to 0.7 were recorded. The time from injection of blocker until the first twitch of the TOF reached 75% recovery was also recorded.

Venous blood samples (4 ml) for measurement of rocuronium concentrations were obtained from the contralateral arm before and 2, 4, 7, 10, 15, 20, 30,

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Table 1 Pharmacodynamics and pharmacokinetics after administration of rocuronium 0.6 mg kg^{-1} in a patient receiving sodium valproate/primidone compared with chronic renal failure patients or healthy patients.[8 9] Cl_{pl} plasma clearance; $T_{1/2}^{\gamma}$=terminal half-life; V^{ss}=volume of distribution at steady state; MRT=mean residence time. CRF=chronic renal failure

	Study patient (CRF)	CRF patients Ref. 8	CRF patients Ref. 9	Healthy patients Ref. 8
Onset (s)	150	61 (25)	63 (17)	65 (16)
25% Recovery of T1 (min)	5.5	55 (27)	54 (22)	42 (9.3)
75% Recovery of T1 (min)	8.5	84 (37)	81 (34)	—
TOF ratio 0 7 (min)	11.3	99 (41)	—	73 (24)
EC_{50} (mg $litre^{-1}$)	2	—	—	—
Cl_{pl} (ml kg^{-1} min^{-1})	14.4	2.5 (1.1)	3.0 (1.3)	3.7 (1.4)
V^{ss} (ml kg^{-1})	246	212 (47)	239 (77)	207 (49)
$T_{1/2}^{\alpha}$ (min)	1.5	1.6 (0.7)		1.8 (15)
$T_{1/2}^{\beta}$ (min)	8.3	24.3 (11.1)		14.8 (5.5)
$T_{1/2}^{\gamma}$ (min)	52	104 (41)	91 (21)	97 (26.4)
MRT (min)	17	97 (49)	—	58 (9.6)

120, 180, 240 and 360 min after the bolus dose of rocuronium. Blood samples were anticoagulated with heparin, iced and centrifuged within 1 h of collection. Plasma was mixed with 0.2 ml of sodium dihydrogen phosphate 0.02 mol $litre^{-1}$ for every 1 ml of plasma, and stored at −30 °C until analysis by high pressure liquid chromatography (HPLC).

Analysis of rocuronium and the metabolites 17-desacetyl-rocuronium and 16-N-desallyl-rocuronium was performed according to the HPLC method of Kleef and colleagues.[6] Intra-day variability of rocuronium in plasma was 5.7% (cv) at 10 ng ml^{-1} and 0.82% at 100 ng ml^{-1}; inter-day variability was 15.2% and 15.8%, respectively. The accuracy of the assay in plasma was 97.0% at 10 ng ml^{-1} and 96.5% at 100 ng ml^{-1}.

Pharmacokinetic variables were calculated from the fitted plasma concentration–time curve after i.v. administration ($r^2 > 0.98$) according to a three-compartment model using the MW/Pharm computer package (Mediware, Groningen, The Netherlands).[7] Elimination half-life ($T_{1/2}$) values were calculated from ln2/β, where β is calculated by log-linear regression analysis of the terminal log-linear phase. $AUC_{0-\infty}$ (area under the plasma concentration–time curve) was calculated using the linear trapezoidal rule, with t being extrapolated to infinity. Total body clearance (Cl) is described as Cl = dose/$AUC_{0-\infty}$. V^{ss}, the volume of distribution at steady state, = $Cl \times$ MRT. $Cl = V^{ss} \times k_{el} = V^{ss} \times 0.693/T_{1/2}^{\gamma}$. Mean residence time (MRT) = $AUMC_{0-\infty}/AUC_{0-\infty}$, where $AUMC_{0-\infty}$ is the area under the moment curve from zero to infinity.

Table 1 shows the main pharmacodynamic and pharmacokinetic variables after rocuronium 0.6 mg kg^{-1} in our patient who was receiving primidone and sodium valproate, compared with published data in control renal failure and healthy patients. Onset time in our patient was 150 s and maximal twitch depression 99%. Figure 1 shows the plasma concentration–time curve of rocuronium in this patient. Total body clearance of rocuronium was 14.4 ml min^{-1} kg^{-1} and the terminal plasma elimination half-life was 52 min. The volume of distribution at steady state in our patient approximated the mean values in the reported studies.

The estimated plasma concentrations of rocuronium in this patient at TOF ratios of 0.7 and 0.9 were 0.85 mg $litre^{-1}$ and 0.58 mg $litre^{-1}$, respectively. The EC_{50} was calculated to be 2 mg $litre^{-1}$. No metabolites of rocuronium were detectable in plasma.

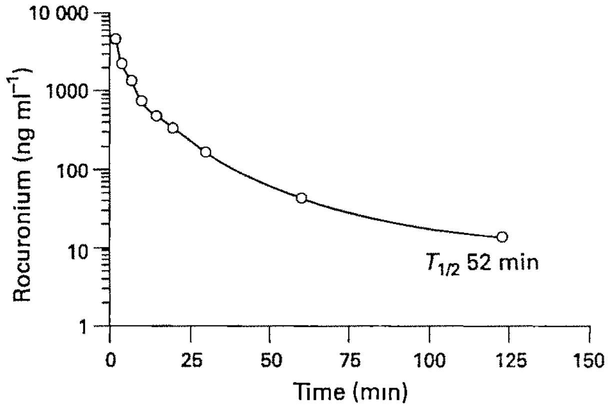

Figure 1 Plasma concentration–time curve (semi-log plot) after administration of rocuronium 0.6 mg kg^{-1} (42 mg) i.v. to a patient with end-stage renal failure receiving chronic anticonvulsant therapy with primidone and valproate No metabolites of rocuronium were measurable. Plasma concentrations of rocuronium at 180, 240 and 360 min were below the limit of quantitation of 10 ng ml^{-1}. $T_{1/2}$ = Terminal plasma elimination half-life (52 min)

Discussion

The clinical duration and recovery of rocuronium 0.6 mg kg^{-1} in our renal failure patient were markedly shorter than in the renal failure patients reported in two previous studies[8 9] or in healthy patients.[8] Clearance of rocuronium in our patient was faster and elimination half-life was shorter than in healthy patients.

A comparable case of decreased duration of action of rocuronium in a renal failure patient receiving chronic therapy with phenytoin has been reported.[9] In that patient, a greatly increased clearance of rocuronium was also found, which could in part be explained by the fact that the patient was still able to produce urine. The authors suggested hepatic enzyme induction by phenytoin as the likely mechanism of the interaction with rocuronium. Loan and collegues[10] also found reduced duration of action of rocuronium 0.6 mg kg^{-1} in patients receiving carbamazepine alone or in combination with other anticonvulsants.

For the observed resistance to non-depolarizing neuromuscular blocking drugs in patients receiving long-term treatment with phenytoin and carbamazepine, three possible mechanisms are reported: (1) increased hepatic metabolism and clearance by enzyme induction[1 9]; metabolites must be included in the overall analysis; (2) increase in protein binding which results in a decreased free fraction of drug to interact with the acetylcholine (ACh) receptor[11 12]; and (3) decreased ACh receptor sensitivity with subsequent up-regulation of the ACh receptor.[11 12]

Our patient was receiving chronic therapy with two other anticonvulsant drugs for which the interaction with neuromuscular blocking drugs is less well studied. Primidone is a prodrug; it is converted to phenobarbital which produces the antiepileptic effects. Primidone (phenobarbital) strongly induces the activity of drug metabolizing enzymes.[13] This is compatible with the high clearance and short elimination half-life of rocuronium in our patient. The elimination pathways of rocuronium remain uncertain, but hepatobiliary elimination is thought to be most important; only 10–30% of an injected dose of rocuronium is eliminated via the kidney.[1] The main metabolic pathway of rocuronium is esterase hydrolysis to 17-desacetylrocuronium. In this patient, plasma concentrations of metabolites were below the limit of quantitation. Thus it appears that rapid elimination and high clearance are unlikely to be caused by increased esterase or enzyme activity. The metabolites 17-desacetylrocuronium or 17-hydroxyrocuronium could be immediately excreted renally or conjugated with glucuronic acid and then excreted. However, this is also unlikely in our patient, as he had renal failure. A similar line of reasoning can be followed for the vecuronium–carbamazepine interaction because vecuronium shows comparable metabolic pathways to rocuronium (3-OH- and 17-OH-vecuronium); therefore, metabolites must be included in the overall analysis to detect increased metabolic elimination.

The actions of atracurium and mivacurium, neuromuscular blocking drugs which are eliminated mainly by plasma esterase and Hofmann degradation, are not affected by co-medication with phenytoin or carbamazepine.[14] However, recovery after doxacurium was twice as fast in patients receiving carbamazepine and phenytoin compared with a control group.[14] Thus vecuronium–rocuronium metabolism must differ from that of atracurium and mivacurium. Enzyme induction is followed by increased liver size and increased liver blood flow. If most of a dose of rocuronium is tightly/covalently bound to this increased number of liver receptor sites, then the apparent increased elimination, without metabolism, may explain the pharmacokinetic variables found in this patient.[15] When these liver binding sites are saturated, for example after long-term infusion in the ICU, then renal excretion becomes more important in the elimination of rocuronium in a similar way as that demonstrated for pancuronium.[16]

Sodium valproate is not an enzyme inducer but its addition to primidone increases serum concentrations of phenobarbital.[13] In contrast, valproic acid may cause up-regulation of the ACh receptor as acute administration in animals causes partial neuromuscular block and potentiates the effects of neuromuscular blocking drugs.[11] In this patient, however, the EC_{50} of rocuronium and plasma concentrations at TOF ratios of 0.7 and 0.9 were within the normal range.[8]

As the clinical relevance and mechanism of the interaction of sodium valproate and primidone with neuromuscular blockers remains unclear, further clinical and experimental study is necessary.

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COMMENTARY

Multicentre evaluation of ryanodine contracture testing in malignant hyperthermia

P. M. Hopkins, E. Hartung, F. Wappler and the European Malignant Hyperthermia Group†

Summary

A common protocol for *in vitro* contracture testing using the plant alkaloid ryanodine has been used by the European Malignant Hyperthermia Group since 1993. This protocol describes a test using 1 µmol/litre of high purity ryanodine (98%) added as a single bolus dose. The main aim of this study was to compare the results obtained with this test between laboratories with a view to assessing the validity of adopting common diagnostic end-points for use in future collaborative studies. In order to do this it was first necessary to determine the optimum cut-off values of the end-points for discriminating between patients diagnosed as susceptible or not to malignant hyperthermia. The end-points under evaluation were expressed in terms of time after application of ryanodine at which a certain degree of contracture develops. In this study, four end-points were investigated: time to initial contracture development (0t); time to development of a 10-mN contracture (10t); time from addition of ryanodine to when baseline tension exceeds pre-drug tension (0tp); and time for contracture to reach 10 mN above pre-drug baseline tension (10tp). This protocol was developed initially and used by three investigating centres and the initial assessment of the end-points and their discriminatory ability was made using the first 100 patients from each of centres 1 and 2, and the first 90 patients from centre No. 3. Optimal cut-off values for each of the end-points were determined using logistic regression analysis. Discriminatory ability was improved by combining the 0t and 10t end-points ($P < 0.05$) but not significantly by combining the 0tp and 10tp end-points. Both methods of categorization were highly sensitive and specific compared with the current standard diagnostic tests. Results from eight additional diagnostic centres which have used the ryanodine contracture test more recently, while indicating that susceptible and normal individuals can be distinguished within a single laboratory, produced a level of variability between testing centres for the ryanodine contracture test that is incompatible with the use of common cut-off values. Possible causes for this variability between laboratories are discussed. (*Br. J. Anaesth.* 1998; **80**: 389–394)

Keywords. malignant hyperthermia; receptors, ryanodine; muscle skeletal, contractility

For more than 25 yr, diagnosis of malignant hyperthermia (MH) susceptibility has been achieved successfully with *in vitro* pharmacological tests on excised muscle strips using separate application of halothane[1] and caffeine.[2] After the recent revolution in the technology of molecular biological techniques, a real possibility has arisen of less invasive DNA-based diagnosis of MH susceptibility. There has been significant progress towards this aim but because of the complexity of the molecular genetics of MH, much more work needs to be done in this area before such a test could be considered reliable enough for safe clinical application.[3] The power of the molecular genetic studies, however, could be increased by improving the specificity of *in vitro* contracture test diagnosis. According to the protocol of the European Malignant Hyperthermia Group for laboratory diagnosis of MH,[4 5] individuals are classified as MH susceptible (MHS) if the muscle has abnormal *in vitro* responses to both halothane and caffeine; they are classified as MH normal (MHN) if their muscle has normal responses to both halothane and caffeine tests; if they respond abnormally to only one of halothane or caffeine they are classified as MH equivocal (MHE). For clinical purposes MHE patients are treated as susceptible to MH, as when there is any doubt over diagnosis the safest course of action is to avoid triggering drugs. It is generally accepted that the MHE group of patients includes some individuals who do not have a genetic predisposition to the disorder.

Ryanodine, a plant alkaloid that was used formerly as an insecticide, produces time- and concentration-dependent contracture of skeletal muscle *in vitro*. Its toxicity is caused by an avid affinity for reticulum calcium release channels[6] which have been subsequently termed ryanodine receptors by pharmacolo-

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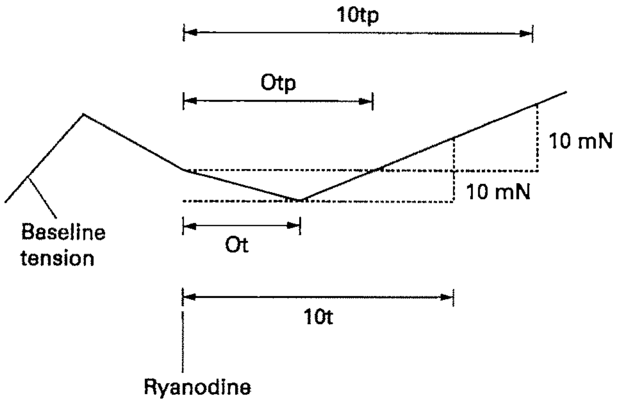

Figure 1 Diagrammatic illustration of the recording from a ryanodine contracture test to show determination of the four end-points evaluated in this study. Measures of early contracture development are time from addition of ryanodine to the first increase in baseline tension (Ot) and time from addition of ryanodine for baseline tension to return to pre-drug tension (Otp). Measures of late contracture development are time from addition of ryanodine to the development of a contracture of 10 mN above the minimum tension (10t) and time from addition of ryanodine to the development of a contracture of 10 mN above pre-drug tension (10tp).

gists. It was demonstrated that in muscle from pigs with porcine stress syndrome, a disorder similar to human MH, there was increased affinity of ryanodine to skeletal muscle calcium release channels compared with channels from muscle of normal pigs.[7] It was suggested subsequently that an *in vitro* contracture test with ryanodine might prove specific for human MH.[8–11] Although absolute sensitivity and specificity has not been achieved with ryanodine contracture testing, it seems likely that the addition of a ryanodine contracture test to the standard halothane and caffeine contracture tests could reduce the number of equivocal results.[12 13] More recently, Hopkins and colleagues[14] have shown that the addition of a ryanodine contracture test improves statistical modelling of contracture test data in order to predict the likelihood of patients being truly susceptible to MH, as would be beneficial for quantitative genetic analyses.

We have evaluated the degree of variability of results obtained with ryanodine contracture testing between laboratories of the European MH Group as a prerequisite to the use of such results in collaborative genetic and other studies. While it is not feasible to establish absolute reproducibility between laboratories because of the impossibility of transporting multiple specimens from single individuals across Europe within the few hours that the muscle remains viable, useful comparisons can be made between different centres by relating results of ryanodine contracture testing to those of the already well standardized caffeine and halothane tests. In the absence of previously agreed end-points for the ryanodine contracture test with which to make comparisons between the 11 centres participating in the study, it was first necessary to establish these and assess how well their use would discriminate between MHS and MHN.

Methods

RYANODINE CONTRACTURE TEST

Muscle bundles (20–30 mm × 2–3 mm × 2–3 mm) were excised from the vastus muscle under regional or trigger-free general anaesthesia. They were maintained in a modified Krebs solution containing (mmol litre^{-1}): NaCl 118.1, KCl 3.4, $MgSO_4$ 0.8, KH_2PO_4 1.2, $NaHCO_3$ 25.0, $CaCl_2$ 2.5 and glucose 11.1 at room temperature and gassed with 95% oxygen–5% carbon dioxide until testing. For contracture testing each muscle bundle was fixed at one end in a tissue bath with the free end of the bundle suspended by a silk suture from a force transducer. The tissue bath contained Krebs solution at 37 °C and was bubbled with 95% oxygen–5% carbon dioxide. The muscle bundle was pre-tensioned and subjected to electrical field stimulation to demonstrate viability: muscle bundles that did not respond to electrical stimulation with a twitch of >10 mN were considered to be non-viable and discarded. After a 10-min equilibration period, ryanodine 1 μmol litre^{-1} (98% pure, Calbiochem, La Jolla, CA, USA) was added to the tissue bath. In seven centres, ryanodine was added as a bolus directly into a relatively large volume tissue bath while in four centres a smaller volume tissue bath was used which was perfused continuously with Krebs solution and ryanodine. Figure 1 is a diagrammatic representation of the four end-points evaluated in this study. The end-points differ in whether or not they refer to early or late contracture development and to the initial reference tension. All end-points were measurements of time and were expressed in minutes. Measures of early contracture development are time from addition of ryanodine to the first increase in baseline tension (Ot) and time from addition of ryanodine until baseline tension exceeds pre-drug tension (Otp). Measures of late contracture development are time from addition of ryanodine to the development of a contracture of 10 mN above the minimum tension (10t) and time from addition of ryanodine to the development of a contracture of 10 mN above the pre-drug tension (10tp).

DETERMINATION OF OPTIMAL CUT-OFF VALUES

Results from ryanodine contracture tests of 290 individuals diagnosed as MHS (n = 101) or MHN (n = 189) in the three diagnostic centres that pioneered ryanodine contracture testing were used. Values for each end-point were used as predictor variables in four separate logistic regression analyses, with MH status as the outcome variable. MH diagnostic status from halothane and caffeine tests was used as the "true" MH status. The optimal cut-off value for each end-point was defined as the value that best segregated ryanodine contracture test results of MHS and MHN patients. This is the value that would give 50% probability of MH susceptibility if entered in the appropriate logistic regression equation. Values for each end-point that define the 95% confidence interval for likelihood of MH susceptibility were also calculated. The proportion of cases in which there was agreement between the standard diagnosis and the ryanodine contracture test end-points is presented.

In order to attempt to optimize the discriminatory ability of the ryanodine contracture test, the two sets of early and late contracture end-points were used to produce further logistic regression models using a backward stepwise selection approach. Thus in one

Table 1 Cut-off values, based on the probability of normality as determined by separate logistic regression models for each of four proposed end-points of the ryanodine contracture test. The optimal cut-off values for each test for distinguishing between MH susceptible and normal individuals was the time predicting a probability of normality of 50%. A ryanodine contracture test result of a time shorter than this optimal cut-off value indicates that the patient is more likely MH susceptible than not, and vice versa

	Time to end-point (min)			
Probability of normality (%)	Ot	10t	Otp	10tp
5	6	17	6	17
50	13	28	16	30
95	19	39	27	41
>99	23	47	33	50

Table 2 Level of agreement of diagnosis of malignant hyperthermia (MH) by the ryanodine contracture test (RCT) by comparison with MH normal (MHN), MH susceptible (MHS) and overall diagnoses obtained using halothane and caffeine contracture tests carried out according to the European MH Group protocol

Criterion for diagnosis of normal by RCT	% Diagnoses correctly predicted		
	MHN	MHS	overall
Ot >13 min	88.12	93.65	91.72
10t >28 min	84.16	94.65	90.97
Otp >16 min	87.13	94.18	91.72
10tp >30 min	82.18	95.14	90.56

of these models the Ot and 10t end-points were used as predictor variables and in the other model the Otp and 10tp end-points were used. For each of these two models an additional predictor variable describing the interaction between early and late contracture end-points was included in order to assess if the relationship between the time to early and time to late contracture development was of any additional value.

ASSESSING CONSISTENCY OF RESULTS IN FURTHER DIAGNOSTIC CENTRES

In these analyses, the ryanodine contracture test results from another 514 individuals were used. Among this group were included patients categorized as MHEc (abnormal result to caffeine only) and MHEh (abnormal result to halothane only) in addition to MHS and MHN individuals. The ryanodine contracture responses of all MHS and MHN patients for each end-point were used for between-centre comparisons using one-way ANOVA with subsequent Scheffé tests. Individual results of the additional patients for each end-point of the ryanodine contracture test were plotted against MH diagnostic status.

Statistical analyses were performed using the SPSS for Windows v6.0 computer package.

Results

The optimal cut-off values determined from the logistic regression analyses and the 95% confidence interval for the likelihood of MH susceptibility for each end-point of the ryanodine contracture test are shown in table 1. Using the optimal cut-off values, the proportion of patients classified as susceptible or not susceptible to MH by the different end-points was in agreement with standard diagnostic tests in more than 90% of individuals in each case (table 2).

When early and late contracture end-point values and their interactions were used as predictor variables in the generation of the logistic regression models, the final model excluded the interaction variable in each case. Table 3 shows the coefficients and their standard errors and significance values that can be used in the logit expression, z, to determine the probability of individual patients being susceptible to MH. In the model using end-points relating contracture development to lowest baseline tension (Ot and 10t), the logistic regression model predicted correctly MH status in 95.83% of patients (a significant improvement on the model derived using only Ot, $P < 0.05$). When the end-point values were derived from contracture relative to pre-drug tension (Otp and 10tp), the ryanodine contracture test model predicted the status correctly in 92.31% of patients.

Comparison of responses of all MHS and MHN patients from the different centres is summarized in figure 2. It is apparent that there were significant differences between mean values for each of the four end-points for several of the centres. From these results certain consistent trends can be observed. For example, early contracture development was delayed in both MHS and MHN muscles tested in centre 1 compared with several other centres, whereas late contracture development was not. Conversely, differences were observed between centre No. 11 and other centres for both early and late contracture variables. Despite these differences, mean values for

Table 3 Details of the coefficients (B), the standard errors of the coefficients (SE) and their significance values (α) generated by the two logistic regression models that used early and late contracture variables as predictor variables. The probability that an individual does not have malignant hyperthermia can be calculated from the results of the ryanodine contracture test using the logistic probability expression,

$$p = \frac{1}{1+e^{-z}},$$

where $z = B_0 + B_1$ (early contracture time) $+ B_2$ (late contracture time)

Contracture variables used in model	Variable								
	Constant			Early contracture variable			Late contracture variable		
	B_0	SE	α	B_1	SE	α	B_2	SE	α
Early variable = Ot Late variable = 10t	−8.25	1.26	<0.01	0.263	0.059	<0.01	0.168	0.059	<0.01
Early variable = Otp Late variable = 10tp	−7.07	0.98	<0.01	0.154	0.038	<0.01	0.148	0.032	<0.01

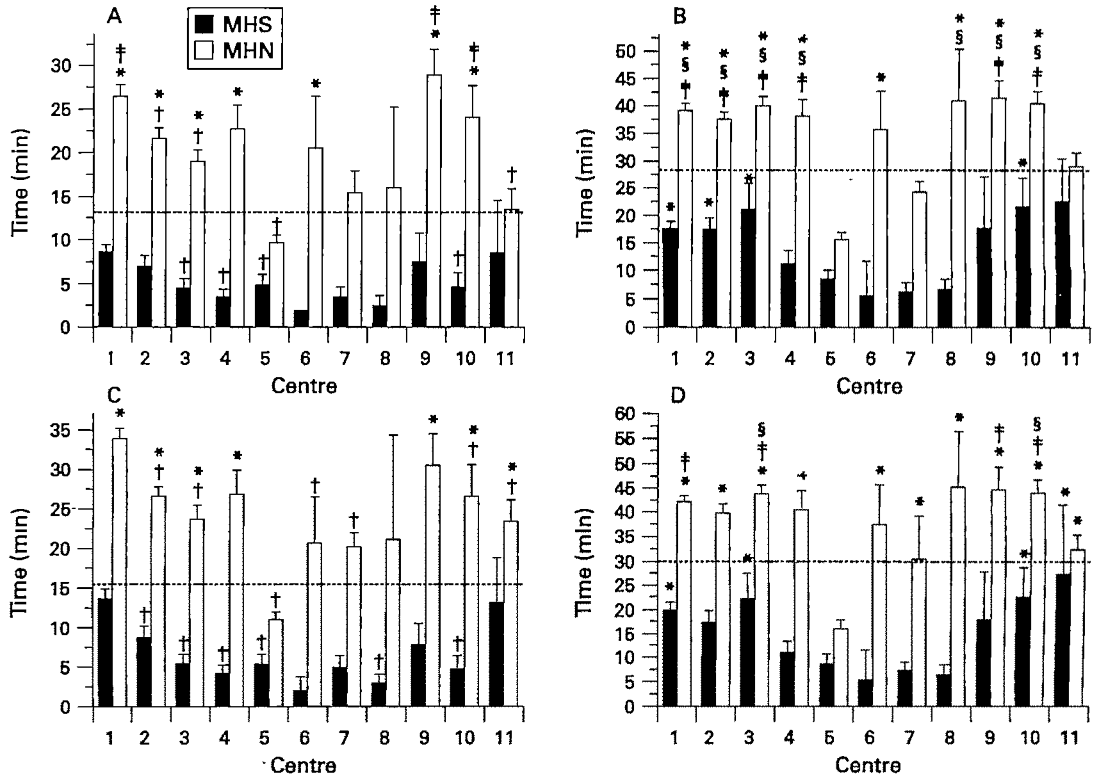

Figure 2 Mean (95% confidence intervals) times for ryanodine contracture responses for four different end-points according to each diagnostic testing centre. The end-points evaluated were: (A) time from addition of ryanodine to the first increase in baseline tension (Ot); (B) time from addition of ryanodine to development of a contracture of 10 mN above the minimum tension (10t); (C) time from addition of ryanodine for baseline tension to return to pre-drug tension (Otp); and (D) time from addition of ryanodine to development of a contracture of 10 mN above pre-drug tension (10tp). MHN = Malignant hyperthermia negative; MHS= malignant hyperthermia susceptible. MHS and MHN results were compared between centres using one-way ANOVA and Scheffé tests, with $P \leq 0.05$ as statistically significant: *compared with centre No. 5, †compared with centre No. 1; ‡compared with centre No. 11; §compared with centre No. 7. The horizontal dotted lines represent the cut-off points above which logistic regression analyses of the results of a subset of 290 patients predicted a greater than 50% likelihood of the patient not having malignant hyperthermia; the upper and lower horizontal dashed lines represent the corresponding 95% and 5% cut-off points respectively.

MHN and MHS muscle responses in each centre were separated by the 50% probability cut-off points derived from logistic regression analysis for each end-point with two exceptions. The 28-min threshold did not separate the mean values for the 10t end-point for MHS and MHN muscles tested by centre No. 7. Of greater concern was that mean values for both MHN and MHS muscles tested by centre No. 5 were below the threshold time for all end-points.

As the results from centre No. 5 were consistently and markedly different from those of the other groups, the results from centre No. 5 were not included in figure 3 in which the results of 446 ryanodine contracture tests studies (excluding patients used in the generation of the models) were compared with the MH diagnostic categories of the patients. It was our intention to conduct further analyses to study the general applicability of the logistic regression models in discriminating between MHS and MHN, but in light of the differences found between the results of different centres, this was felt to be inappropriate.

Discussion

The main aim of this study was to assess the between-centre variation in results obtained using a standardized protocol for ryanodine contracture testing in the diagnosis of malignant hyperthermia. In order to evaluate variability it was necessary initially to determine cut-off values for the different end-points that have been proposed by individual groups on the basis of their own pilot studies.[10 11] The protocol for ryanodine contracture testing used in this study has been adopted by the European MH group after agreement between the MH units in Leeds, Würzburg and Hamburg which pioneered ryanodine contracture testing in MH in Europe. The concentration of ryanodine used (1 μmol litre^{-1}) was agreed as the best compromise between attempts to improve discrimination between MHS and MHN muscles and the practical consideration of how long each test took to conduct. Using this protocol we have shown that it is possible to discriminate between MHS and MHN individuals, as diagnosed by standard *in vitro* contracture testing with caffeine and halothane, in more than 90% of patients. Better discrimination is achieved by combining results of early and late contracture development, although no significant difference between the two approaches in determining the end-point values was detected in this study.

The logistic regression analysis used in this study not only enabled objective determination of cut-off values for the different end-points but it also provided a means of improving the discriminatory power of the ryanodine contracture test and a means of estimating the likelihood of MH susceptibility from a given ryanodine contracture test. The validity of such estimations does, however, assume that results obtained by laboratories other than those used in the generation of the logistic regression equations are from the same population. We found significant differences

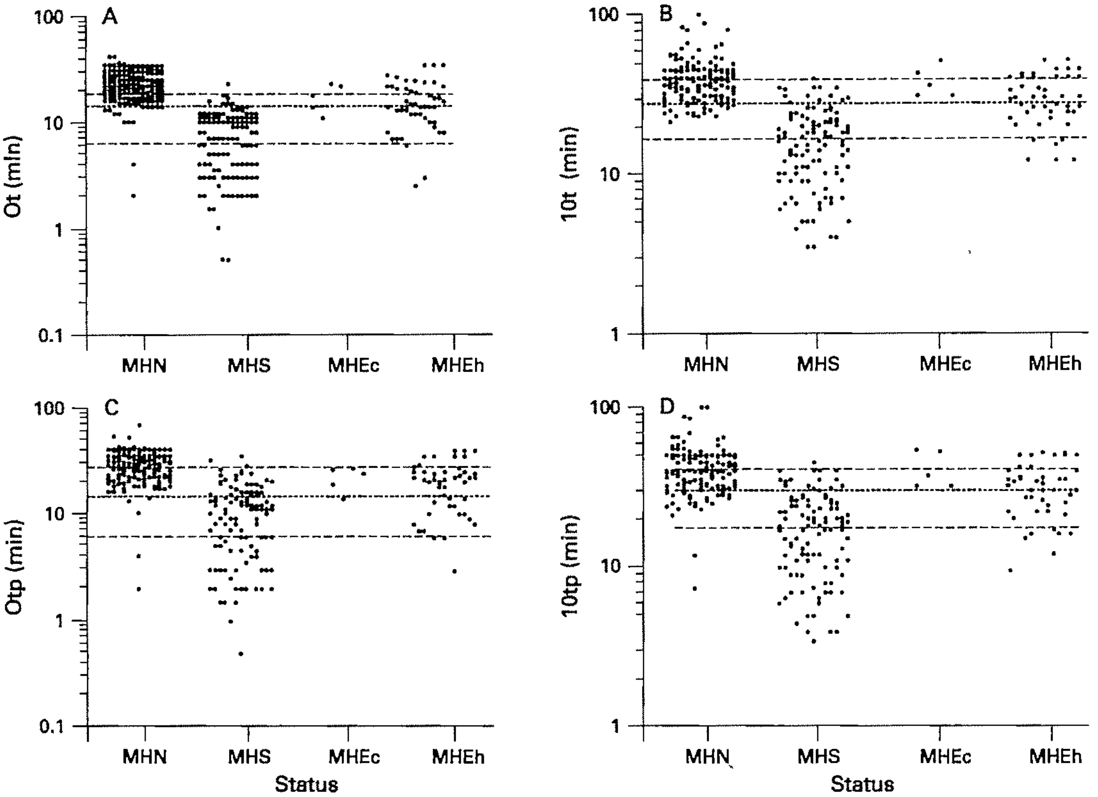

Figure 3 Distribution of ryanodine contracture test results for the four different end-points compared with diagnostic status indicated by conventional contracture testing for 446 patients. The end-points evaluated were: (A) time from addition of ryanodine to the first increase in baseline tension (Ot); (B) time from addition of ryanodine to development of a contracture of 10 mN above the minimum tension (10t); (C) time from addition of ryanodine for baseline tension to return to pre-drug tension (Otp); and (D) time from addition of ryanodine to development of a contracture of 10 mN above pre-drug tension (10tp). MHN = Malignant hyperthermia negative; MHS = malignant hyperthermia susceptible; MHEc = malignant hyperthermia equivocal, abnormal response to caffeine only; MHEh = malignant hyperthermia equivocal, abnormal response to halothane only. Data points may represent more than one patient. The horizontal dotted lines represent the cut-off points above which logistic regression analyses of the results of a different set of 290 patients predicted a greater than 50% likelihood of the patient not having malignant hyperthermia: the upper and lower horizontal broken lines represent the corresponding 95% and 5% cut-off points, respectively.

in ryanodine responses between several centres, and in some cases these were large enough to compromise the use of common variables for discriminating between "normal" and "abnormal" ryanodine contracture responses. The degree of variability in ryanodine contracture results between the different laboratories suggests that it would be inappropriate to define common cut-off values until the reasons for the variability are clarified.

The reason for the disparity between the results of the different centres is not yet apparent. There are some methodological differences in the way ryanodine contracture testing was conducted in the different laboratories. For example, in eight centres, a separate dedicated tissue bath was used for ryanodine contracture tests, while in three it was not; in seven centres ryanodine was added as a bolus directly into a relatively large volume tissue bath while in four centres a smaller volume tissue bath was used which was perfused continuously with Krebs solution and ryanodine. Also, in six centres the ryanodine contracture test was performed simultaneously with the halothane and caffeine tests while in the other five centres it was not. While it would be ideal for all centres to use exactly the same methodology, these differences do not correlate with the differences found in ryanodine contracture test results.

However, there is an analogous situation with the diagnostic halothane and caffeine tests. In these tests, common threshold concentrations of halothane and caffeine are used successfully by all centres, but the size of contracture developed at threshold concentrations varied between centres (European MH Group, unpublished data). It is possible that such differences may be a result of inherent population differences. It is now known for example, that the prevalence of different mutations associated with MH susceptibility varies between countries and regions.[15] As with the ryanodine contracture test, however, these findings are perhaps more suggestive of inadequate standardization of the contracture testing protocols. That such inter-laboratory variation has apparently not been a problem with the halothane and caffeine tests is perhaps a reflection of the robust nature of the current diagnostic criteria, but it may also explain partly the necessity for the equivocal group defined by these criteria.

We have compared the ryanodine contracture test with results obtained using standard halothane and caffeine diagnostic tests. With this approach it is not possible to say if the overlap obtained between MHS and MHN groups was caused by less than perfect discriminant ability of the ryanodine contracture test or if it was the standard diagnostic tests that were wrong. When considering the ability of the ryanodine contracture test to determine the true MH status of patients characterized as MHE by halothane and caffeine tests alone, it can be seen from figure 3 that this is possible in a proportion of MHE patients. The proportion of MHE patients it is possible to re-classify depends on the degree of certainty, or confidence, that is required of the MH diagnosis. This in turn is a reflection of the use of the diagnostic procedure. For example, for clinical use a very high degree of confidence is required before labelling an individual as MH normal as the consequences of a false negative diagnosis are potentially most serious. On the other hand a lesser degree of confidence is required for the ryanodine contracture test to confirm an MHE individual as being likely to be truly susceptible to MH. The logistic regression model approach can be used as a refinement for phenotypic characterization of MH family members for use in genetic linkage studies.[14] In this case the addition of a ryanodine contracture test could be used to estimate the probability of a particular phenotype when other tests produce indeterminate results.

It was not our intention to assess if ryanodine contracture tests could possibly replace the caffeine or halothane tests, or even both, in MH diagnostics. In order to do that it would be necessary to conduct all three types of test on a large series of individuals who, from the details of their clinical reaction, could be deduced to be almost certainly truly susceptible to MH (e.g. by the method of Larach and colleagues[16]) and also another series of individuals who are at low risk for the condition.[17] Initial results from such investigations, albeit with relatively small numbers of patients, are promising in that no overlap between ryanodine contracture responses in low and high risk groups has been found.[10 11] In common with previous work, we conclude that the ryanodine contracture test protocol used in this study can usefully discriminate between MH susceptible and normal individuals but the degree of variability between results from different centres cautions against the use of common diagnostic cut-off values. Greater standardization of techniques used by the European MH Group laboratories in the performance of *in vitro* contracture tests is required and, until this is achieved, each laboratory should be encouraged to define its own cut-off values for the ryanodine contracture test.

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CITATION CLASSIC

Commentary

Johnstone M. The human cardiovascular response to Fluothane anaesthesia. *British Journal of Anaesthesia* 1956; **28**: 392–410.

It would be difficult to overstate the significance for anaesthetic practice of the synthesis of halothane in 1951 by Suckling and its first use in clinical anaesthesia by Johnstone in 1956. This event probably represented the biggest pharmacological advance in anaesthesia since the introduction of neuromuscular blocking agents into anaesthesia in 1942 by Griffith and Johnson. Before 1956, the most commonly used volatile anaesthetic agent was ether. With its relatively high therapeutic ratio, it could be given safely by the less experienced using uncalibrated vaporizers but the lower therapeutic ratio of halothane demanded further technological advances in anaesthesia, including the development of calibrated anaesthetic vaporizers. Its administration via low flow circle systems necessitated the development of readily available and inexpensive volatile gas monitors, and the use of this non-explosive anaesthetic agent also permitted the huge expansion in electronic monitoring devices which occurred in the two decades subsequent to its introduction.

This article by Johnstone represents a fine example of the high quality clinical observations made by his contemporaries and the early eminent pioneers of anaesthesia. Although embroidered by a vast number of subsequent clinical investigations and research, many of his observations remain as pertinent today as they did in 1956. For example, he observed that halothane induced dose-dependent hypotension in association with bradycardia. He ascribed this to depression of the sympathetic nervous system with sparing of the parasympathetic nervous system; consequently, many of these changes could be antagonized by administration of atropine. He also noted that cardiac arrhythmias occurred during halothane anaesthesia, although they were uncommon, possibly because of routine premedication with atropine. Ventricular arrhythmias occurred more commonly in the presence of hypercapnia and many responded to increased alveolar ventilation, although Johnstone did not appreciate that the mechanism was a reduction in Pa_{CO_2}.

Many other aspects of this article serve to remind us of the considerable advances which have taken place in anaesthesia in the past three decades. Interpretation of the supposedly beneficial effects of cutaneous vasodilatation awaited the ability to monitor arterial $P\text{co}_2$ rapidly and easily; the importance of flow as opposed to pressure is not evident in this article. Subsequently, modern assessment of the cardiovascular system with measurement of cardiac output, filling pressures in the heart and direct arterial pressure has revealed that halothane has no effect on peripheral vascular resistance and that hypotension is produced largely by direct myocardial depression. But these changes may be attenuated to some extent during spontaneous respiration as a result of the hypercapnia induced by the powerful respiratory depressant effects of halothane.[1]

Johnstone exhibits little appreciation of the effect of IPPV on venous return and the reliance on a pure α adrenergic agonist, methoxamine, to maintain arterial pressure would now be regarded as illogical.

Other non-cardiovascular observations made by Johnstone have stood the test of time, for example the low incidence of nausea and vomiting, absence of stimulation of secretions, and smooth induction and recovery from anaesthesia. Tachypnoea induced by all volatile agents is diminished by administration of opioids and this was noted by Johnstone: only the peculiar description of diuresis after halothane anaesthesia was unfounded.

Today, the use of halothane is declining rapidly in advanced Western countries because of concern regarding its hepatotoxicity.[2] The fact that the number of deaths induced by halothane per annum in the UK has always remained small in relation to the deaths caused by paracetamol poisoning, bears witness to the inherent safety of halothane anaesthesia. However, the continued availability of paracetamol "over the counter" but restriction in use of halothane reflect the demands put upon anaesthetists to strive for perfection and total safety; this is preventing the continued use of the drug because of medico–legal fears in the event that jaundice follows halothane anaesthesia. None the less, halothane is still used widely in many countries and the drug is used frequently in experimental investigations of the cellular effects of anaesthetics.

This article of Johnstone's may therefore have no more relevance today than to serve as an example of the value of good clinical observations. However, it marks a milestone in the development of anaesthesia, not only with regard to a major clinical pharmacological advance, but also the subsequent development of anaesthetic gas delivery and monitoring systems and the start of a period of rapid growth in our physiological and pharmacological understanding of anaesthesia.

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THE HUMAN CARDIOVASCULAR RESPONSE TO FLUOTHANE* ANAESTHESIA

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TRIFLUOROETHYL vinyl ether (Fluoromar) was the first fluorinated volatile compound to be used in clinical anaesthesia (Krantz, et al., 1953; Orth and Dornette, 1955). Its lower limit of inflammability was 3 per cent of the vapour. Prior to this a series of fluorinated compounds was investigated by Robbins (1946) who observed that the anaesthetic potency of a fluorinated compound was greatly increased by the insertion of a second halogen atom. This work has been extended by Raventós and Suckling (1956) and the compound CF_3-CHClBr (2 : bromo 2 chloro 1 : 1 : 1 : trifluoro ethane) was found to have excellent anaesthetic properties in animals as well as being nonexplosive and noninflammable when mixed in high concentrations with oxygen. This compound will be referred to as Fluothane.

Fluothane is a colourless liquid with a specific gravity of 1.86 at 20° C. and its boiling point is 50.2° C. at 760 mm Hg pressure. Its vapour pressure is 439 mm Hg at 20° C. Vapour concentrations within the anaesthetic range have a pleasant and nonirritant odour. The compound is decomposed by light but is stable if stored in amber-coloured bottles; the action of light is prevented by thymol 0.01 per cent w/w. Decomposition does not take place in the presence of warm soda lime.

The pharmacology of Fluothane has been investigated in detail by Raventós (1956). It is about four times as potent as di-ethyl ether with a therapeutic ratio about twice that of ether. Surgical anaesthesia can be rapidly induced in animals with from 2 per cent to 4 per cent of the vapour in oxygen and maintained for several hours on 1 per cent with excellent relaxation and spontaneous respiration. Recovery of consciousness is rapid—two to ten minutes—even after prolonged anaesthesia. Salivary and mucous secretions were abolished in nonatropinized animals and neither retching nor vomiting occurred during induction, maintenance, or recovery from anaesthesia. Cardiac irregularities did not appear during any phase of anaesthesia though ventricular tachycardia and ventricular fibrillation were precipitated by the intravenous injection of adrenaline and noradrenaline to dogs anaesthetized with the drug.

A consistent finding in most animals was a fall in blood pressure which was directly proportional to the concentration of Fluothane vapour inhaled. This effect has been related to a block of the sympathetic ganglia with splanchnic vasodilation. The hypotensive effect was minimal with the 1 per cent vapour concentration used for maintenance.

Histopathological studies revealed minor cytological changes in the livers and kidneys of experimental animals after prolonged Fluothane anaesthesia. These changes did not appear to be associated with significant functional or biochemical alterations.

In view of the rather attractive pharmacological properties of this drug a clinical trial was begun. This paper is a report on the effect of Fluothane on some 500 patients. The list of operations performed on them is given later. Some of the patients would come under the heading of "good risks", whilst others could be described as "grave risks" and a still greater number would fall into intermediate categories. This initial report will be concerned mainly with the cardiovascular effects of Fluothane when administered from a Boyle's apparatus.

METHOD

The smaller (Trilene) bottle of a Boyle's apparatus was found to provide a vapour concentration of from 0.2 to 4.2 per cent at 25° C. with a gas flow of 10 litres a minute, Fluothane filled to the 100ml mark, and the plunger fully withdrawn. Under similar circumstances with 50 ml of Fluothane in the bottle the vapour range was 0.1 to 2.8 per cent. With the plunger fixed at 3 mm above the surface of the liquid the vapour range was 0.6 to 4.8 per cent.

It is obvious that only approximate values of vapour concentrations can be obtained when using this equipment for prolonged anaesthesia. In recording the strength of Fluothane vapour used in the clinical trial I will refer to a mark on the extended scale (fig. 1B) which was fixed alongside the control lever of the bottle and gives the approximate vapour concentration as calculated from a chart provided for this particular vaporizer. In all cases the 10-litre gas flow remained constant and consisted of 5 litres of oxygen and 5 litres of nitrous oxide; the plunger was always fully withdrawn; and the liquid maintained approximately at the 50 ml mark.

Blood pressures were estimated by sphygmomanometry and radial pulse palpation in all cases before induction and at frequent intervals thereafter. Respiratory rates were recorded at frequent intervals. Continuous electrocardiography was used

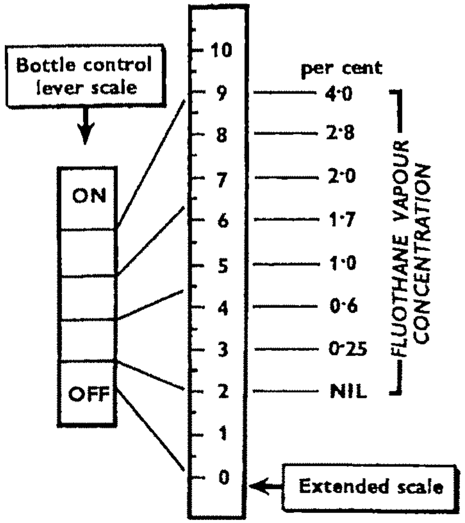

FIG. 1A

Diagram of the extended scale showing the vapour concentrations available at 25°C with 100 ml of Fluothane in the bottle, the plunger fully withdrawn, and a gas flow of 10 litres a minute.

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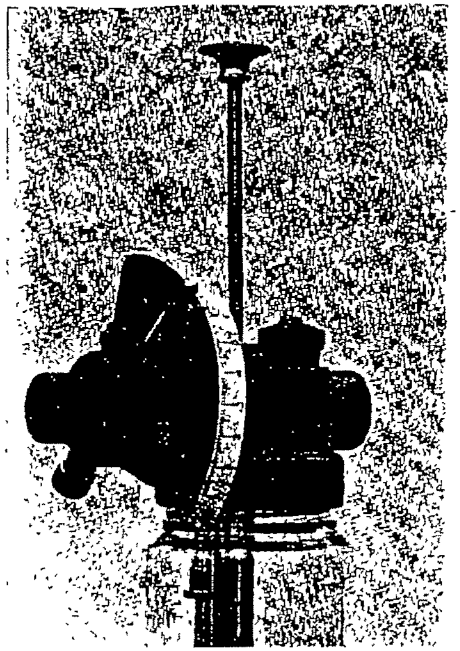

FIG 1B
Photograph of vaporizer showing extended scale fixed alongside the control lever

during most major operations; cardiograms were obtained of disturbances of rhythm which occurred before or during the administration of the anaesthetic.

Premedication.

Atropine only, 0.6 mg thirty minutes before induction .. .. 108 cases
Atropine 0.6 mg with pethidine 50 mg before induction .... 392 cases

Induction of Anaesthesia.

In all cases, except where otherwise stated, anaesthesia was induced with a sleep dose of thiopentone (250 mg) injected intravenously followed by 50 mg of suxamethonium and oropharyngeal or orotracheal intubation. The induction of anaesthesia with Fluothane will be made the subject of a separate study and report.

Series One Vapour concentration 2.2 to 3.2 per cent approximately; lever mark 7 to 8; plunger fully withdrawn; 50 ml of Fluothane in the bottle.

This initial series consisted of fifty adults with normal cardiovascular and respiratory systems undergoing operations such as herniorrhaphy, mastectomy, thyroidectomy (nontoxic), varicose vein, and various orthopaedic procedures. Each operation lasted a minimum of twenty-five minutes and took place with the patient in the supine position. Each patient was premedicated with atropine 0.6 mg and pethidine 50 mg and an airway inserted under the thiopentone-suxamethonium sequence. Respiration was then controlled with oxygen, nitrous oxide and Fluothane (mark 7 or 8) until the return of spontaneous respiration a few minutes later. Anaesthesia was then maintained with a similar mixture till the end of the operation.

Smooth anaesthesia persisted throughout the period of operation in all cases, without narcotic or relaxant supplementation. Adequate relaxation was always present. The respiratory rate tended to increase during Fluothane anaesthesia and particularly with surgical stimulation, the average rate during the operations being 28 respirations a minute. The transition from suxamethonium apnoea to spontaneous respiration under Fluothane anaesthesia was made without coughing or straining In each case reflex activity returned within two or three minutes of stopping the anaesthetic and was followed by a five- to ten-minute period of apparently natural sleep from which the patient resented being roused. Full consciousness then returned and was not associated with any restlessness, retching, or vomiting; none of the patients complained of nausea.

The administration of Fluothane vapour in this concentration range caused a rapid fall in blood pressure within two or three minutes of starting. In 35 cases the systolic pressure dropped to between 60 and 80 mm Hg and the hypotension was associated with brisk vasodilatation with an increase in the volume of the peripheral pulse; the skin became warm, dry, and pink, and remained in this state throughout the period of anaesthesia. There was no capillary oozing from the cut tissues though the larger vessels bled normally.

As the blood pressure fell during Fluothane anaesthesia the pulse rate invariably became slower and rates as low as 45 beats a minute were observed. Atrioventricular nodal rhythms were seen in five patients, atrioventricular dissociation with interference in two, and an unusual form of sinus arrhythmia with coupling of sinus beats was seen in two patients (fig. 2B). In all these cases sinus rhythm was restored by the intravenous administration of atropine 0.5 mg. This dose of atropine also raised the systolic pressure from 60 to 80 mm Hg in three patients.

In most cases the hypotensive effect persisted throughout the period of anaesthesia. In eight cases the systolic pressures, after initial falls to 80 mm Hg, rose gradually to 100 mm Hg and persisted at this level for the remainder of the operations.

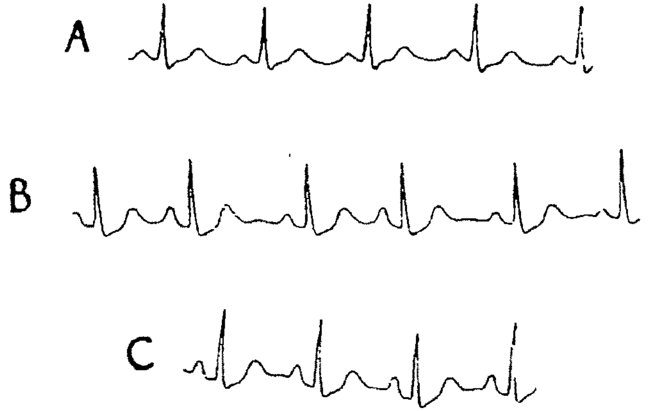

FIG 2

Male, 48 years Fit and muscular Nephrectomy for stone Premedicated with atropine 0 6 mg with pethidine 50 mg All Lead 2

A Before induction

B. After thirty minutes Fluothane (scale mark 8) anaesthesia, note the unusual coupling of the sinus beats.

C Thirty seconds later, after atropine 0 5 mg intravenously

In nine patients the hypotension outlived the narcosis by twenty minutes. There were no increases in pulse rates during the recovery periods, and in several patients the rates tended to decrease as the blood pressures returned to normal.

Series Two. Vapour concentration 0.75 to 1.25 per cent approximately; lever mark 6 to 7; plunger fully withdrawn; 50 ml of Fluothane in the bottle.

Fifty patients, with normal cardiovascular and respiratory systems, undergoing operations similar to those in the previous series. Each patient was premedicated with atropine 0.6 mg and pethidine 50 mg administered intramuscularly thirty minutes before induction. An additional dose of 0.5 mg of atropine was mixed with the sleep dose of thiopentone, suxamethonium 50 mg injected and an airway inserted. Anaesthesia was then maintained with oxygen, nitrous oxide 50 per cent, and Fluothane (1 per cent approximately). This concentration provided smooth and even anaesthesia with adequate spontaneous respiration and sufficient relaxation for all the operations. The respiratory rates increased to an average of 30 a minute; this rate could be reduced to any required level by the intravenous administration of pethidine in doses up to 40 mg. The recovery phases were similar in all respects to those in the previous series, except that one patient vomited a few times and two complained of nausea. The patient who vomited stated that she became nauseated shortly after the pethidine was administered pre-operatively and she vomited twice before the induction of anaesthesia. During cold weather it was noted that several patients shivered for a few minutes after recovering consciousness; the shivering required no specific treatment.

The incidence of hypotension was considerably less in this series. The systolic pressures fell to 70 mm Hg in six patients and in the remainder the average systolic pressure during the maintenance of anaesthesia was 100 mm Hg. The mild hypotension associated with Fluothane (1 per cent approx.) anaesthesia persisted throughout the period of anaesthesia in most cases, but in sixteen patients the systolic pressures gradually returned to within normal limits after thirty minutes anaesthesia. A perfectly regular sinus rhythm persisted throughout anaesthesia in all cases, the average rate being 84 beats a minute. Heart rates in general tended to decrease slightly as the operation progressed, and there were no reactionary tachycardias in any patients during recovery from anaesthesia. Throughout the period of anaesthesia in each case the skin remained warm, dry, and pink, with prominent superficial veins. The cardiograms showed no significant changes in the ST segments or T waves.

PRELIMINARY CONCLUSIONS

The results obtained in this series indicated that Fluothane provided very smooth and easily reversible anaesthesia with adequate relaxation for the operations selected. Although relaxation was of a high degree there was no obvious evidence of respiratory depression with the vapour concentrations used. The effects on the cardiovascular system—hypotension and bradycardia—were consistent with a depression of sympathetic activity with sparing of the cardiac parasympathetic mechanism—a syndrome very similar to that induced by high spinal analgesia. Other signs suggestive of depression of autonomic activity were the persistent vasodilatation, the complete absence of sweating, the complete suppression of salivary, bronchial, and gastric secretions, and the absence of vomiting and retching in the recovery period.

It is obvious that the intensity of the cardiovascular reaction to Fluothane anaesthesia is directly related to the vapour concentration used, being minimal with the 1 per cent which appears to be the concentration needed for maintenance in most cases. Many of the patients felt quite hungry and were able to enjoy substantial meals within two or three hours of the operations. There were no obvious signs of postoperative damage to kidneys, livers, or lungs, though the effects of Fluothane on the functions of these organs will be the subject of more detailed investigations.

In view of the encouraging results obtained in the preliminary studies, the use of Fluothane was immediately extended to cover most types of surgical operations on patients with either normal or abnormal cardiovascular and respiratory systems. The only patients excluded were those with obviously diminished blood volumes pre-operatively. An additional 400 cases have now been completed, their ages ranging from 7 months to 86 years. Premedication was either atropine 0.6 mg alone or combined with pethidine 50 mg; anaesthesia was induced with a sleep dose of thiopentone (unless otherwise stated) and an airway inserted under suxamethonium paralysis. The additional 0.5 mg of atropine was usually injected with the thiopentone and omitted only when tachycardia was present or when hypotension was considered to be necessary to limit bleeding, e.g. neurosurgery, mastectomy, etc. Fluothane was used in the vapour concentration range of 0.75 to 1.25 per cent (scale marks 6 to 7) with nitrous oxide and oxygen 50 per cent. Details of the operations for which Fluothane was the main anaesthetic used are as follows:

ABDOMINAL SURGERY	139	cases
Cholecystectomy	28	
Cholecyst-duodenostomy	7	
Gastrectomy, partial	23	
Gastro-enterostomy, with vagotomy	15	
Hemicolectomy	12	
Splenectomy	6	
Adrenalectomy, bilateral	4	
Colostomy	12	
Appendicectomy	27	
Resection of rectum, abdoperineal	5	
GENITO-URINARY SURGERY	129	cases
Prostatectomy, suprapubic	46	
Prostatectomy, per urethral	24	
Cystoscopy, with diathermy, etc.	37	
Nephrectomy	11	
Nephrolithotomy	8	
Nephrostomy	1	
Diverticulum of bladder	1	
Cystectomy, total	1	
ORTHOPAEDIC SURGERY	31	cases
Compression screws, neck of femur	2	
Trauma	3	
Fractures, reduction and fixation	10	
Amputations	16	
HERNIORRHAPHY	23	cases
NEUROSURGERY	29	cases
Craniotomy	15	
Laminectomy	6	
Radiography	5	
Carotid ligation	3	
MASTECTOMY (radical)	17	cases
THYROIDECTOMY	23	cases
Toxic	16	
Nontoxic	7	
GYNAECOLOGY	4	cases
Caesarean section	1	
Colporrhaphy	3	
CHEST SURGERY	5	cases
Mitral valvotomy	3	
Cardiac neurectomy	2	

Fluothane provided excellent relaxation for all these cases with the exception of the laparotomies, some of which required supplementation with relaxants. Adequate spontaneous respiration was present throughout the operations and seldom required any assistance. In the majority of patients the administration of Fluothane caused an increase in the respiratory rate, the depth remaining either unaltered or slightly increased. Surgical stimulation, particularly in the region of the anus, often caused an increase in the respiratory rate, and rates up to 60 a minute have been encountered during haemorrhoidectomy. These rapid rates were not associated with any increase in the resistance of the lungs to inflation nor was there any increase in the tone of the abdominal musculature such as occurs during trichlorethylene tachypnoea. Tachypnoea not associated with anal stimulation can be controlled with pethidine in doses up to 40 mg; that associated with anal stimulation is effectively abolished by suxamethonium.

Brisk reflex activity returned in two or three minutes after stopping the Fluothane in all cases and vomiting during recovery was present in about 4 per cent of patients, being most evident after cholecystectomy. Transient postoperative nausea was present in 8 per cent of the patients.

Fluothane in the concentration range of 0.75 to 1.25 per cent caused a moderate drop in blood pressure in most cases and a drop to 90 mm Hg in 10 per cent of cases. After twenty or thirty minutes anaesthesia the systolic pressure gradually returned to within normal limits in about half of these patients. Anaesthetized patients were often sensitive to changes in posture, and the reversed Trendelenburg position sometimes precipitated a profound hypotension. Sudden loss of blood during anaesthesia was associated with a sudden fall in the systolic pressure without much change in the pulse rate; the reaction to the transfusion of blood or saline was rapid. Traction on abdominal viscera or retraction of brain tissue caused sudden drops of blood pressure with slowing of the pulse rate in about 20 per cent of the patients subjected to these manœuvres.

Essential hypertension, which was present in eighteen patients, caused no significant alterations in the cardiovascular reactions to Fluothane.

The hypotension associated with Fluothane anaesthesia can be prevented or immediately abolished by the intravenous injection of methoxamine hydrochloride (Cummings and Hays, 1956) in 5-mg doses. This drug has invariably produced the desired effect and is much more consistent in its vasopressor action than other drugs of this type. It has not caused any cardiac arrhythmias or tachycardias when administered to patients anaesthetized with Fluothane. The dose should be carefully restricted, as excessive amounts—10 mg and over—may cause severe hypertension. Methoxamine completely prevents the hypotension associated with the head-up position.

Cardiac Rhythm during Fluothane Anaesthesia.

Sinus rhythm has persisted at a steady rate throughout anaesthesia in most cases. Atrioventricular nodal rhythm was extremely rare, probably as the result of the additional atropine administered with the thiopentone during the induction of anaesthesia. The sinus rate has seldom shown any tendency to increase even after periods of anaesthesia up to 270 minutes nor has there been any increase during and after the recovery of consciousness. Ventricular extrasystoles were observed in twelve cases and were either of the isolated variety or coupled with sinus beats (bigeminy); in each case the arrhythmia was associated with impairment of ventilation either as the result of positioning—steep Trendelenburg or lateral positions—or by respiratory depression from relaxants, and in each case was quickly abolished by assisting the respiration.

The operations of thyroidectomy for thyrotoxicosis and bilateral adrenalectomy for carcinomatosis have not been associated with any disturbance of cardiac rhythm during Fluothane anaesthesia. The application of the electric cautery to haemorrhoids and to bleeding points in the prostatic bed has precipitated transient sinus tachycardia with isolated ventricular extrasystoles in four patients, the cardiovascular disturbance being associated with brisk tachypnoea. The reactions have not been observed during Fluothane anaesthesia when the nerve supply to the region has been blocked by a "saddle-block" spinal analgesic.

The shock syndrome—sinus tachycardia, hypotension, vasoconstriction, sweating, and delayed recovery of consciousness—has not been seen in any patient either during anaesthesia with Fluothane or after the recovery of consciousness. Delayed circulatory collapse—24 to 48 hours postoperatively—occurred in three patients after major surgery and is suspected to be related to hypokalaemia.

Relaxants and Fluothane.

The use of relaxants to facilitate the exploration of the peritoneal cavity is probably advisable when using Fluothane anaesthesia. Attempts to produce with Fluothane in all cases the complete paralysis of the abdominal musculature nowadays expected by the surgeons may result in unnecessarily severe degrees of hypotension requiring postural adjustments.

In the initial stage of this part of the investigation 15 mg of d-tubocurarine were injected intravenously into each of ten patients anaesthetized with Fluothane (scale mark 7); laparotomy for appendicitis was being performed on each and the d-tubocurarine was injected as the peritoneum was being incised. Following the injection of d-tubocurarine in each case there was an immediate drop in blood pressure to between 60 and 70 mm Hg. without significant change in the pulse rate.

Controlled respiration was then necessary in three patients, and in one of these the peripheral pulse disappeared completely during positive pressure inflation of the lungs, and a cyanotic pallor developed; the slightest pressure on the rebreathing bag obliterated the carotid pulse which returned slowly and sluggishly when the pressure was withdrawn. The appendicectomy was hurriedly completed and neostigmine 2 5 mg with atropine 0.5 mg were administered intravenously. As soon as spontaneous respiration commenced there was a dramatic improvement in the patient's circulation: the systolic pressure rose to 70 mm Hg and the pulse was easily palpable at the wrist. Three minutes later a severe bradycardia with hypotension recurred—neostigmine effect—and was modified by a further 0.5 mg of atropine; consciousness returned in fifteen minutes and the systolic pressure became normal two hours later; subsequent recovery was uneventful. Similar syndromes of somewhat less alarming degrees occurred during controlled respiration in the other patients. All patients seemed to be hypersensitive to the inhibitory effects of neostigmine on the heart and required unusually large doses of atropine to counteract this effect.

For the subsequent twenty adult laparotomies the dose of d-tubocurarine was restricted to 5–10 mg, depending on the size of the patient. This dosage produced satisfactory relaxation with spontaneous respiration which required assisting in a few cases. Two mitral valvotomies were successfully performed with this technique, using only assisted respiration throughout; in both these cases the relaxation provided by the Fluothane (scale mark 6½) was quite adequate, the d-tubocurarine being given to depress a little the spontaneous respiration. Neostigmine was considered necessary for a few cases in this series and severe bradycardia occurred in spite of a reasonable dose of atropine. In view of the consistent hypersensitivity to the cardio-inhibitory effects of neostigmine the further use of d-tubocurarine during Fluothane anaesthesia was abandoned.

Suxamethonium in 50 mg doses intravenously was then administered during Fluothane anaesthesia. It caused no further fall in systolic pressure, in fact the systolic pressure frequently increased by from 10 to 15 mm Hg. Similarly, controlled respiration during suxamethonium apnoea under Fluothane (scale mark 7) did not produce any obvious impairment of the peripheral circulation. Over 200 patients have now received suxamethonium 50 mg intravenously under Fluothane anaesthesia without any adverse effects on their cardiovascular systems. In the management of abdominal cases a small dose of suxamethonium (30 to 50 mg) is given intravenously as the peritoneum is incised so as to permit the easy exploration and exposure of the pathological viscus. Subsequent doses are seldom required until the closure of the peritoneum when the suxamethonium is repeated, the Fluothane providing adequate relaxation and spontaneous respiration for the major part of the operation.

Heart Disease and Fluothane Anaesthesia.

Seventeen patients with clinical and electrocardiographic evidence of myocardial disease secondary to coronary insufficiency—eight of them had angina of effort and six had previous histories of congestive heart failure—have been anaesthetized with Fluothane (scale mark 6¼) for periods up to two hours. The operations included prostatectomies, cholecystectomies, and hemicolectomies. Throughout the periods of anaesthesia there was no significant evidence of further myocardial damage and all the patients recovered uneventfully. One of these patients had a severe anginal attack on arrival at the operating theatre and the details of the case are as follows:

Case 1. Male, 48 years. Muscular and well nourished. For transthoracic cardiac neurectomy for the relief of intractable angina of effort. The electrocardiogram showed inverted T waves in the six V leads, with erect T waves in the classical limb leads. No cyanosis, oedema, or arteriosclerosis Lungs normal. Blood pressure 120/85. Premedicated with atropine 0.6 mg and pethidine 50 mg. A few minutes after arrival at the theatre the patient complained of severe precordial pain and dyspnoea. His pulse rate was 115 beats a minute and his blood pressure 120/80, and the electrocardiogram showed depression of the ST segment on lead 2 (fig 3A) Anaesthesia was immediately induced with thiopentone 200 mg intravenously (without additional atropine) followed by suxamethonium 50 mg and orotracheal intubation; this caused no change in the electrocardiogram Anaesthesia was then maintained with oxygen, nitrous oxide 50 per cent, and Fluothane (scale mark 7). Smooth spontaneous respiration returned in three minutes by which time the pulse rate had dropped to 88 beats a minute and was of much better volume, the systolic pressure had fallen to 70 mm Hg; the skin became warm, dry, and pink, and the ST segment returned to its normal isoelectric position (fig. 3D). Fifteen minutes later, just prior to the opening of the pleural cavity, 7.5 mg of d-tubocurarine were administered intravenously and respiration gently assisted to prevent the complete collapse of the left lung For the next twenty minutes anaesthesia was maintained with Fluothane (scale mark 6¼), the systolic pressure persisted at 70 mm Hg, the pulse rate gradually slowing to a steady 65 beats a minute, and the skin remaining warm and dry. Fluothane was then discontinued and within five minutes, although the pulse rate and blood pressure were gradually rising, the skin became clammy and cool. Fluothane (scale mark 6¼) was started again and in a few minutes the skin became warm and dry, the blood pressure stabilized at 70 mm Hg systolic and the pulse rate at 65 beats a minute. The operation was successfully completed after 80 minutes anaesthesia. Methoxamine hydrochloride 5 0 mg was injected intravenously at the end of the operation. Fifteen minutes later the patient was awake and rational with a blood pressure of 130 mm Hg systolic and a pulse rate of 88 beats a minute. Recovery was uneventful.

Eleven patients with electrocardiographic evidence of hypertensive heart disease have been anaesthetized with Fluothane for periods up to 2¼ hours without the development of any significant evidence of further myocardial damage. In these patients the systolic pressure did not fall below 100 mm Hg. The following case history illustrates one

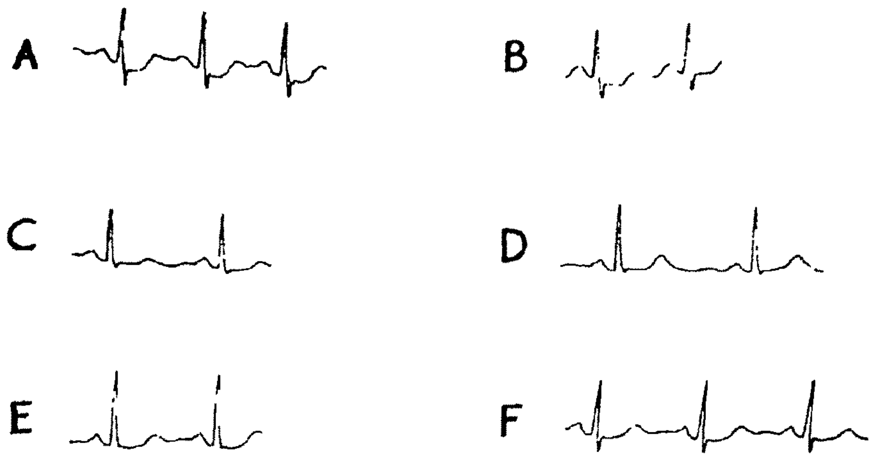

Fig. 3

Case 1. See text for clinical details. All Lead 2

A. Immediately before induction
B. After intubation under thiopentone and suxamethonium
C. Three minutes later, under Fluothane anaesthesia
D. After Fluothane anaesthesia for thirty minutes
E. After Fluothane anaesthesia for sixty minutes, lighter plane.
F. Fifteen minutes after the end of the operation; patient conscious.

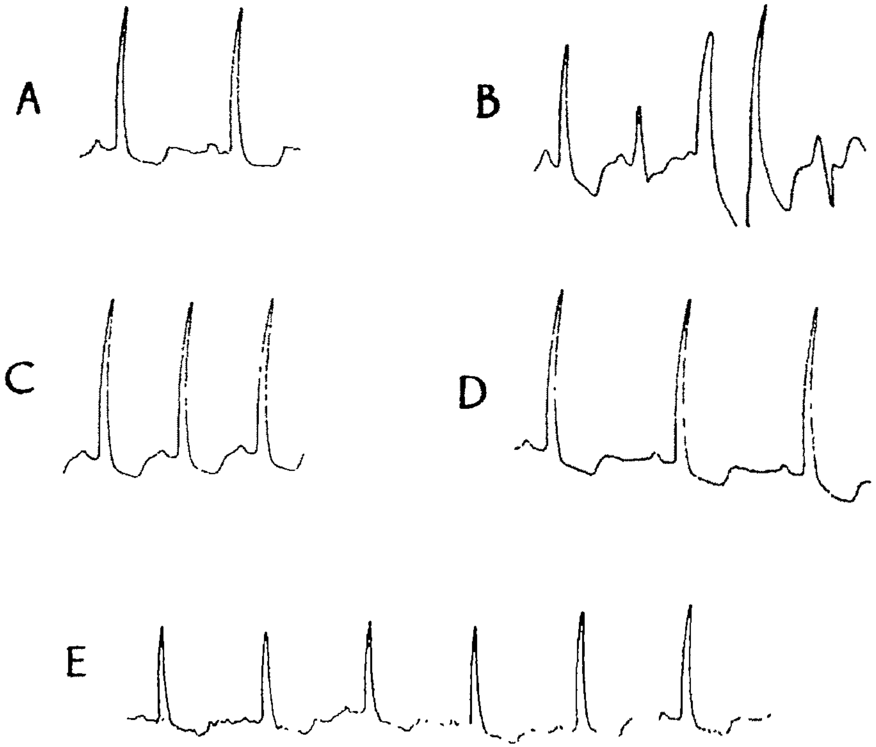

Fig. 4

Case 2 See text for clinical details All Lead 1

A. Before induction
B. Immediately after induction with thiopentone; patient well oxygenated
C Twenty seconds later, after the insufflation of Fluothane vapour
D After Fluothane anaesthesia for two hours.
E Twenty minutes after the end of the operation, patient conscious

of the more severe hypertensives during Fluothane anaesthesia:

Case 2 Female 66 years Craniotomy and removal of a right frontal glioma. Frail and thin Fully conscious Blood pressure 210/120 with electrocardiographic evidence of hypertensive heart disease (fig 4A) No cyanosis or oedema, lungs normal Premedication atropine 0 6 mg with pethidine 50 mg Induced with thiopentone (without additional atropine) followed by suxamethonium 50 mg and orotracheal intubation A severe derangement of cardiac function followed the injection of thiopentone (fig 4B) and was abolished immediately (fig. 4C) by the rapid insufflation of Fluothane vapour (2 per cent approx in oxygen). the patient was adequately oxygenated at the time of the appearance of this arrhythmia. Anaesthesia was then maintained for 2¼ hours with oxygen nitrous oxide 50 per cent, and Fluothane (scale mark 6). During the period of anaesthesia the systolic blood pressure did not drop below 130 mm Hg and bleeding from the operation area was negligible Blood replacement therapy was not necessary and the patient responded to instructions within fifteen minutes of the conclusion of the operation Recovery was uneventful

Effects of Fluothane on Cardiac Arrhythmias present before Induction.

Auricular fibrillation was present in eight patients before induction. The fibrillation was associated with coronary sclerosis in two patients, mitral stenosis in one patient, pulmonary emphysema in three, and thyrotoxicosis in two patients. Throughout the operations the auricular fibrillation was unchanged and the ventricular response decreased in each case. All patients made uneventful recoveries.

Frequent ventricular extrasystoles were observed in seven patients before operation. In six of these the ectopic beats disappeared completely during Fluothane anaesthesia but returned with the return of consciousness; one of these cases is illustrated in figure 5. The incidence of ectopic beats in the seventh case remained unchanged during the induction, maintenance, and recovery from anaesthesia.

Pulmonary Disease and Fluothane Anaesthesia.

Twenty-eight patients with chronic hypertrophic pulmonary emphysema have

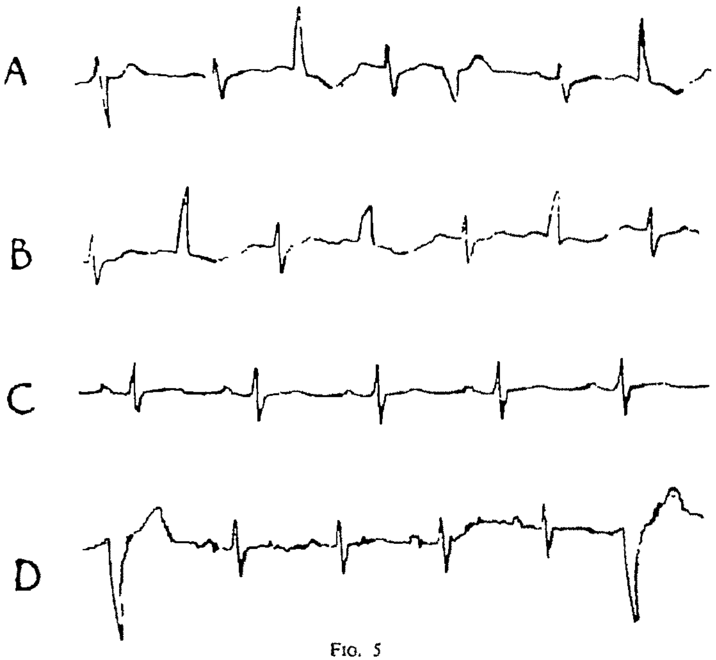

Fig. 5

Female, 75 years For removal of a rectal polyp. Irregular pulse No oedema or cyanosis Blood pressure 140/90 Premedicated with atropine 0 6 mg with pethidine 50 mg All Lead 2

A Before induction
B After thiopentone 200 mg intravenously
C After five minutes Fluothane anaesthesia
D During recovery of consciousness

been anaesthetized with Fluothane. In one case the pulmonary disease was secondary to severe kyphoscoliosis, the remainder being due to chronic bronchitis. Three of these patients had severe cor pulmonale syndromes with orthopnoea, cyanosis, and congestive heart failure at intervals. The operations were mainly prostatectomies. Each patient was premedicated with atropine and pethidine and anaesthesia was induced with the usual sleep dose of thiopentone followed by suxamethonium 50 mg and the insertion of an airway; one patient was induced with Fluothane (scale mark 8) in oxygen. In each case the Fluothane anaesthesia was associated with smooth and easy respiration with the disappearance of the bronchiolar constriction associated with the disease; cyanosis disappeared and the patients became pink and well oxygenated; muscular relaxation was excellent and bleeding was minimal. Recovery of consciousness was prompt in all cases and there was no evidence of the shock syndrome. In the more severe cases there appeared to be an improvement in their respiratory functions postoperatively. Clinical details of one of these cases are as follows:

Case 3 Male, 43 years Haematuria and pyuria due to prostatic calculi Severe kyphoscoliosis with cor pulmonale Cyanosed, orthopnoeic, and confined to bed for the past six months; occasional oedema of the dependent parts Blood pressure 130/90: Sinus rhythm, 125 beats a minute, with severe right ventricular strain

First anaesthetic Cystoscopy Induced with thiopentone 250 mg intravenously followed by suxamethonium 50 mg and the insertion of an airway Apnoea persisted for the next thirty minutes during which time the patient was ventilated with nitrous oxide in oxygen 30 per cent, during this period the pulse was rapid and feeble, the systolic blood pressure 70 mm Hg and sometimes much lower A cyanotic pallor persisted throughout the period of anaesthesia and was associated with clammy sweating Weak spontaneous respiration returned after thirty minutes and consciousness returned twenty-five minutes later. The patient was very distressed and dyspnoeic for several hours afterwards.

Second anaesthetic. Three months later, Fluothane now available. For suprapubic prostatectomy Patient's cardiopulmonary condition unchanged Patient arrived at the theatre in a severely orthopnoeic state, cyanosed and sweating, pulse rate 125 a minute, blood pressure 135/90, electrocardiograph showed sinus tachycardia with right ventricular strain (fig. 6A) Anaesthesia was induced with Fluothane (scale mark 8). After two minutes the patient was obviously unconscious but not adequately relaxed for easy intubation; 50 mg of suxamethonium were immediately injected intravenously and an orotracheal tube inserted without difficulty and without electrocardiographic disturbance. During the period of suxamethonium apnoea the patient's lungs were very difficult to inflate but this difficulty disappeared with the return of spontaneous respiration three minutes later For the next 90 minutes anaesthesia was maintained smoothly with Fluothane (scale mark 7). During this time respiration was spontaneous and offered no resistance to inflation. The systolic blood pressure was maintained at 70 mm Hg, with a regular sinus rhythm at 110 beats a minute (fig 6B). Relaxation was excellent and bleeding was minimal—the operation was performed with the patient in the Trendelenburg position 30 degrees. Throughout the operation the patient's skin remained warm, dry, and pink Consciousness returned within fifteen minutes of stopping the anaesthetic and recovery was uneventful. After the operation the patient stated that his breathing felt easier than it had done for several months.

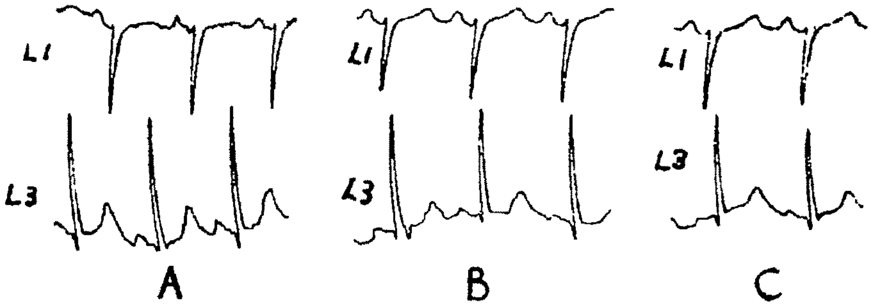

Fig 6

Case 3. See text for details Leads 1 and 3

A. Before induction
B. After Fluothane anaesthesia for forty minutes.
C. During the recovery of consciousness

In addition to the emphysematous patients there were three patients with suppurative bronchiectasis and three with active pulmonary tuberculosis. There were no operative or postoperative pulmonary complications in any of these patients. During anaesthesia with Fluothane there was a complete absence of salivary, mucous, and bronchial secretions in these patients.

Jaundice and Fluothane Anaesthesia.

Eight adult patients with jaundice have been anaesthesized with Fluothane for periods up to two hours. In seven patients the jaundice was due to carcinoma of the head of the pancreas and cholecystduodenostomy was done in each case; two of these patients had hypertensive heart disease, one with auricular fibrillation and intraventricular block. The eighth patient became jaundiced after an attack of acute cholecystitis. Each patient was premedicated with atropine 0.6 mg with pethidine 50 mg and anaesthesia was induced with the usual dose of thiopentone—with additional atropine—followed by suxamethonium 50 mg and orotracheal intubation. Anaesthesia was then maintained with Fluothane (scale mark 7). Maintenance of anaesthesia was smooth and uneventful in all cases, without any clinical or electrocardiographic evidence of further cardiovascular damage; recovery of consciousness was as quick as in the nonjaundiced cases. Seven patients made uneventful recoveries, the jaundice gradually disappearing in two or three weeks; one patient, with carcinomatous deposits in the liver, died on the seventh postoperative day from the effects of biliary peritonitis.

Uraemia and Fluothane Anaesthesia.

Fluothane (scale mark 6 to 7) was administered to ten patients with uraemia secondary to urinary obstruction due either to prostatic hypertrophy or to ureteric obstruction by pelvic neoplasm. In addition, twelve elderly males were admitted with uraemia secondary to prostatism; normal blood urea levels were restored in each of these cases by preoperative catheter drainage. Details of the patients who were still uraemic at the time of operation are as follows:

Case 4 Female, 48 years. Anuria of at least 48 hours duration, secondary to obstruction of both ureters by pelvic neoplasm. Blood urea 380 mg per cent; serum potassium 6.54 mEq ; blood pressure 170/100 mm Hg Patient drowsy and dehydrated, radial arteries difficult to palpate, suggesting vasospasm of considerable degree, no visible or palpable veins on arms or legs Premedicated with atropine 0.6 mg and pethidine 50 mg

Anaesthesia was induced with Fluothane (scale mark 8) and an orotracheal tube inserted without difficulty and without electrocardiographic changes after two minutes (fig. 7B). Anaesthesia then maintained for the next 45 minutes with Fluothane (scale mark 6½), during which time a left nephrostomy was performed without difficulty, relaxation being excellent, bleeding minimal, and spontaneous respiration remaining efficient

Immediately after the induction of anaesthesia the systolic blood pressure dropped to 70 mm Hg and brisk vasodilatation occurred with the appearance of several large veins on the forearms which permitted the easy intravenous administration of fluids and glucose to combat the potassium intoxication The electrocardiogram, which pre-operatively showed evidence of potassium intoxication (fig 6A) remained completely unchanged throughout the operation

Consciousness returned five minutes after the cessation of Fluothane inhalations and the blood pressure returned to 170 mm Hg systolic a few minutes later. There was no postoperative nausea or vomiting Immediately after the operation there was a steady flow of urine from the nephrostomy and three days later the blood potassium was subnormal (fig 7), this was rectified by the oral administration of potassium The blood urea, after a gradual rise to 440mg per cent on the third day after the operation, had returned to normal by the 21st postoperative day

Case 5. Female, 51 years Anuria for two days as the result of ureteric obstruction by pelvic neoplasm. Fully conscious, condition good, blood urea 120 mg per cent, serum potassium normal Induced and maintained with Fluothane for thirty minutes during which time urinary flow was re-established by the insertion of ureteric catheters Blood chemistry gradually eturned to normal in seven days

Case 6 Female, 53 years Clinical details essentially similar to Case 5. After twenty minutes of Fluothane anaesthesia, a pre-operative blood urea of 153 mg per cent had returned to normal a week later

Case 7 Male, 75 years. Acute retention of urine due to prostatic hypertrophy Completely disorientated and confused, blood urea 135 mg per cent. Heart and lungs normal Anaesthesia induced with thiopentone 250 mg (with additional atropine) and maintained by Fluothane (scale mark 7) for 65 minutes whilst a suprapubic prostatectomy was successfully performed. Consciousness returned fifteen minutes after the end of the operation and there was no evidence of shock. Twenty-four hours later the patient was quite rational and the blood urea returned to normal seven days later.

Case 8. Male, 83 years, with prostatic hypertrophy. Blood urea 243 mg per cent on admission and reduced to 87 mg per cent after four weeks catheter drainage A suprapubic prostatectomy was successfully performed under Fluothane anaesthesia lasting 55 minutes Postoperatively there was a progressive rise of the blood urea level to 350 mg per cent on the 15th day, this was associated with a diuresis and normal blood electrolytes most of the time Seven days later the blood urea had returned to 83 mg per cent and the patient had become ambulant and active.

Case 9. Male, 68 years. with prostatic hypertrophy. Blood urea on admission was 123 mg per cent and reduced to 74 mg per cent by seven days catheter drainage Suprapubic prostatectomy then performed under Fluothane anaesthesia. Postoperatively the blood urea rose to 112 mg per cent on the third day and was within normal limits by the tenth day

Case 10. Male, 79 years. Clinical details essentially similar to Case 9.

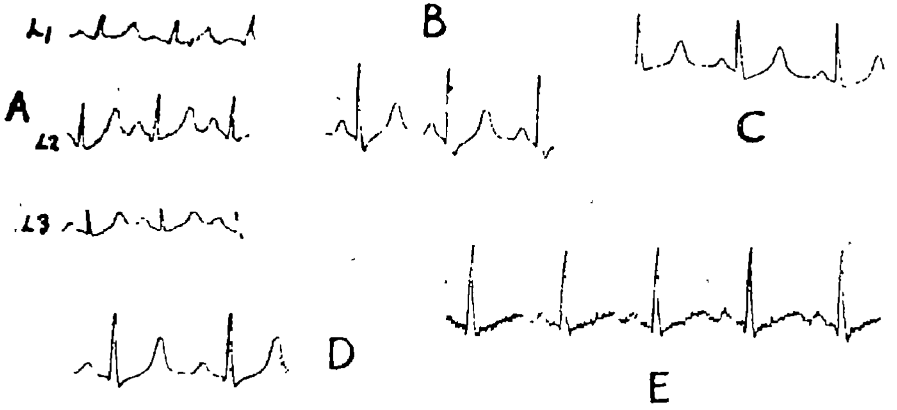

Fig. 7

Case 4 See text for clinical details. All. except A, are Lead 2.

A Before induction. Leads 1, 2, and 3. Serum potassium 6 54 mEq
B After induction and intubation under Fluothane anaesthesia
C. After forty minutes of Fluothane anaesthesia
D During the recovery of consciousness
E. Three days later Serum potassium 3.08 mEq.

Case 11. Male, 67 years Clinical details essentially similar to Case 9.

Case 12 Male, 63 years Clinical details essentially similar to Case 9

Case 13 Male, 68 years Clinical details essentially similar to Case 9

Deaths following Surgery under Fluothane Anaesthesia.

No deaths have occurred under Fluothane anaesthesia. Six patients have died in the postoperative period and the details are as follows:

(1) Female. 47 years Bilateral adrenalectomy for generalized carcinomatosis due to malignant disease of the breast Pathological fractures of the ribs. pleural effusions, and multiple secondaries in the liver. Emaciated and anaemic The bilateral approach to the adrenals was used and the patient tolerated the operation very well Blood pressure remained within normal limits throughout and consciousness returned five minutes after the completion of the operation Twenty-four hours later the blood pressure began to fall and the patient died twenty hours later in spite of the intensive use of vasopressors of various kinds.

(2) Male. 61 years Died seven days after a suprapubic prostatectomy. Autopsy revealed bilateral suppurative pyelonephritis and old standing suppurative bronchiectasis Cause of death was toxaemia due to sepsis

(3) Male, 68 years. Amentia secondary to cerebral atrophy as the result of cerebral arteriosclerosis Bedridden and incapable for several months Scattered moist sounds at both lung bases Cerebral angiography and pneumoencephalography performed under Fluothane anaesthesia of 65 minutes duration. Consciousness and full reflexes returned within fifteen minutes without any evidence of shock or collapse. Prior to recovery of consciousness a considerable amount of purulent sputum was aspirated from the bronchi The patient died 48 hours later from what appeared to be hypostatic pneumonia. Autopsy revealed a terminal bronchopneumonia

(4) Baby, seven months old For removal of a huge occipital meningoencephalocele Heart and lungs normal. Premedicated with atropine 0 4 mg. Anaesthesia induced with Fluothane (scale mark 8). Intubation of the trachea was impossible because of the extreme degree of neck flexion caused by the tumour A nasopharyngeal tube was inserted and anaesthesia smoothly maintained for the next 2½ hours with Fluothane (scale mark 7) During this time the meningocele was excised along with a large amount of brain tissue Blood loss was moderately severe and was not satisfactorily replaced. The baby commenced to cry and move its limbs within five minutes of stopping the anaesthetic Death occurred twelve hours later and permission for autopsy was not obtained.

B

(5) Male. 73 years Cystoscopy and suprapubi prostatectomy Fit and well nourished Heart and lung normal, blood pressure 170/100. Blood urea 83 m per cent Twenty-six years history of diabetes mellitus having insulin 20 units twice daily with appropriat diet Blood sugar immediately before operation wa 240 mg per cent No urinary evidence of ketosis Premedicated with atropine 0 6 mg and pethidin 50 mg Anaesthesia induced with thiopentone 250 m (with additional atropine 0 4 mg) followed by suxa methonium and the insertion of an airway. Th operation was performed under Fluothane (scal mark 6½) without difficulty in 75 minutes, relaxatio was adequate without relaxants, bleeding was minimal and the systolic blood pressure did not drop belo 110 mm Hg Blood transfusion was not required Recovery from anaesthesia was complete in fiftee minutes

Twelve hours later the patient became restless an the blood sugar rose to 480 mg per cent. The appro priate therapy was instituted, but the response wa unsatisfactory, and the patient died from wha appeared to be peripheral circulatory failure 36 hour later During the first 24 hours postoperatively ther was a satisfactory urinary output Hypokalaemia wa not excluded Autopsy failed to reveal the cause o death

(6) Female, 41 years Craniotomy and partial re moval of a pituitary tumour. Obese Heart and lung normal Premedicated with atropine and pethidine Anaesthesia induced and maintained for 3½ hours wit Fluothane Consciousness returned within fiftee minutes after the end of the operation and the patient condition was excellent for the next twenty-four hours A sudden and unexpected collapse then occurred an the patient died within a few minutes. Autopsy faile to reveal the cause of death.

DISCUSSION

The general picture of the huma cardiovascular system during Fluothan anaesthesia is one of vasodilatation com bined with hypotension and bradycardia The vasodilatation—as evidenced by dry warm, and pink skin with prominen superficial veins—becomes obvious withi a few seconds after the start of inhalation and persists throughout the period o anaesthesia, even when minimal concen trations of vapour are inhaled. It does no appear to be affected by haemorrhage o by surgical stimuli

The hypotensive effect is directly re lated to the inhaled vapour concentration being minimal with the lower concentra tions used for the maintenance of anaesthesia. In just less than half of the patients the hypotensive effect diminished as the anaesthetic continued: whether this is due to an increasing tolerance to the drug or to a diminishing output by the vaporizer cannot be stated but it is obvious that, for a drug of this potency, much more accurately controlled and calibrated vaporizers should be incorporated in the anaesthetic apparatus. Sudden haemorrhage causes an immediate and precipitous fall in systolic pressure, and the response to intravenous transfusion of blood or saline is equally rapid. The hypotensive effect of Fluothane can be safely prevented or abolished by the intravenous administration of methoxamine, if considered necessary. Patients under Fluothane anaesthesia are particularly sensitive to the vasopressor effects of methoxamine and doses in the region of 5 mg are usually adequate.

The use of d-tubocurarine with controlled respiration would appear to be contra-indicated during Fluothane anaesthesia. It would seem that d-tubocurarine, which is known to depress synaptic conduction in the sympathetic ganglia (Langley, 1918; Robbins and Lundy, 1947), in these circumstances causes such a profound degree of sympathetic block that intermittent positive pressure respiration obstructs the flow of blood through the lungs with consequent collapse of the systemic circulation.

Some degree of slowing of the pulse rate has always followed the administration of Fluothane, even to patients premedicated with atropine 1.0 mg. The mechanism of the slowing is not yet fully understood, but it is undoubtedly based on overactivity of the cardiac vagus. Whether this vagal overactivity is due to active stimulation of the parasympathetic nerves to the heart, or to an increase in vagal tone secondary to depression of the normal sympathetic counteraction, remains to be seen. Until further knowledge is obtained it would seem to be advisable to premedicate all patients with atropine in the appropriate dosage.

Light Fluothane anaesthesia has produced only minimal electrocardiographic evidence of increased irritability of the human heart. Twelve patients developed ventricular extrasystoles during the maintenance of light anaesthesia in circumstances in which the elimination of carbon dioxide was obviously impaired. Several other patients were subjected to similar degrees of ventilatory impairment and failed to show any electrocardiographic evidence of arrhythmia. Ventricular tachycardia has not been observed in any patient.

The most striking effect of Fluothane anaesthesia has been the complete absence of the shock syndrome—tachycardia, hypotension, sweating, pallor, and vasoconstriction—during and immediately following surgical operations. This was particularly evident after the more severe operations and especially in patients with advanced cardiovascular and respiratory diseases. Postoperative hypotension persisted for one or two hours in three patients in whom the replacement of blood loss was either inadequate or tardy; nevertheless, their skins remained warm and dry, their pulse rate averaged 90 beats a minute, and the recoveries of consciousness were not retarded.

The apparently complete protection which Fluothane anaesthesia has provided against surgical shock in this investigation may be related to a suppression of sympathetic activity during anaesthesia. Evidence is accumulating which indicates that blockade of the sympathetic division of the autonomic nervous system during surgery prevents the type of circulatory collapse which may lead to death (Martin, 1955; Overton and De Bakey, 1956; Ross and Herczeg, 1956; Hershey et al., 1956). The excellent results obtained with Fluothane anaesthesia in patients with severe pulmonary emphysema and cor pulmonale may also be related to its effects on sympathetic ganglia: Bromage (1956) has recently demonstrated that ganglionic blockade caused significant increases in the vital capacities of patients with pulmonary hypertension.

As the result of recent clinical observations it has been suggested that Fluothane anaesthesia may be followed by a diuresis which may cause hypokalaemia in those patients whose potassium levels are already diminished by disease. Although the evidence is by no means complete, it would be advisable to ensure adequate electrolytic and fluid replacements in those patients who present evidence of electrolytic depletion prior to or after anaesthesia with Fluothane.

One elective Caesarean section was successfully performed under Fluothane (scale mark 7½) anaesthesia. Relaxation was adequate, bleeding minimal, the child was fully conscious when delivered from the uterus, and the uterus retracted normally after the removal of the placenta. Recovery of consciousness was complete in seven minutes after the removal of the face mask and there was no evidence of shock, vomiting, retching, or nausea.

SUMMARY

(1) Fluothane—a new nonexplosive volatile anaesthetic agent—has been administered to 500 patients, including many with cardiovascular, pulmonary, renal, and hepatic diseases complicating the surgical lesions. Each patient was premedicated with atropine, either alone or combined with pethidine, and anaesthesia was induced in most cases with a sleep dose of thiopentone.

(2) Smooth and rapidly reversible anaesthesia has been maintained in all cases by the continuous administration of Fluothane vapour, using a Boyle's vaporizer and a gas flow of ten litres a minute with 50 per cent oxygen and nitrous oxide.

(3) Cardiovascular changes suggestive of depression of sympathetic activity have consistently been observed and which, to a certain extent, were modified by atropine and by the strength of the vapour concentration inhaled. The shock syndrome has been completely absent in all cases.

(4) There has been a complete absence of salivary, mucous, and bronchial secretions in all cases throughout the period of anaesthesia. Nausea, vomiting, and retching during recovery have been absent in over 90 per cent of the patients.

(5) Cardiac arrhythmias of the vagal type were observed when the higher concentrations of Fluothane vapour were inhaled. These arrhythmias included sinus bradycardia, atrioventricular nodal rhythms often with interference, dissociation, and an unusual form of sinus

arrhythmia with coupling of the sinus beats. Atropine restored normal sinus rhythms in these cases. Their incidence has been completely eliminated by adequate atropinization.

(6) Ventricular arrhythmias have been observed only in the presence of inadequate ventilation in lightly anaesthetized subjects and were of a mild degree. Ventricular tachycardia has not been observed.

(7) Cardiovascular collapse—slow pulse and profound hypotension—has followed the combined use of d-tubocurarine and controlled respiration on patients anaesthetized with Fluothane. Such reactions did not occur when suxamethonium and controlled respiration were used in conjunction with Fluothane anaesthesia.

(8) Tachypnoea has occurred during surgical stimulation in patients lightly anaesthetized with Fluothane. The reaction can be controlled by pethidine or by regional nerve block.

(9) No deaths have occurred under anaesthesia. The details of six postoperative deaths have been presented.

(10) It has been suggested that Fluothane anaesthesia may cause an immediate postoperative diuresis which may lead to serious electrolytic depletion in those patients already in a state of electrolytic deficiency as the result of disease.

ACKNOWLEDGMENTS

I should like to express my sincere thanks to Dr Suckling of the General Chemicals Division of Imperial Chemical Industries Ltd, Widnes, for providing supplies of Fluothane. and also to Dr Raventos and Dr Paget of Imperial Chemical (Pharmaceuticals) Ltd., Manchester, for their constant assistance. I am also most grateful to my surgical colleagues at the Royal Infirmary and at Crumpsall Hospital, Manchester, for their co-operation

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CORRESPONDENCE

Anaesthesia after exhaustive exercise

Sir,—There are no reports on the effect of preceding exhaustive exercise, such as marathon running, on the course of anaesthesia. We report an extreme case. A healthy 21-yr old (65 kg, 173 cm) active jogger (40–60 km/week) presented for day-case tonsillectomy under general anaesthesia. Three days earlier he had run his first marathon and told the anaesthetist that his legs were painful. He had difficulty in lying down on the operating table. After operation, he told us that after 30 km of the marathon he had become so exhausted that he could remember little of the rest of the race.

An i.v. anaesthetic was used, supplemented with 70% nitrous oxide in oxygen. The drugs given and their total doses were as follows: glycopyrrolate 0.2 mg, propofol 280 mg, fentanyl 300 µg and rocuronium 50 mg. Residual neuromuscular block was antagonized at the end of operation with neostigmine 2.5 mg and glycopyrrolate 0.5 mg. During surgery, 2500 ml of crystalloid i.v. solutions were given. Postoperative analgesia was achieved with ketoprofen.

After operation the patient was able to breathe satisfactorily but despite normal responses to peripheral nerve stimulation he appeared extremely weak, that is he was unable to lift his head or even his hand. Because his condition had not improved after 6 h, he was moved to the local university hospital. Thirteen hours after operation the patient had to be escorted to the toilet by two people. Next morning he was able to walk but still complained of muscle pain, especially in his legs. The muscle pain disappeared gradually over the next 3 days.

Eight hours after operation total blood count, C-reactive protein concentrations, serum concentrations of creatinine, sodium, potassium and chloride, and blood-gas analysis, serum lactate, ammonium ion and insulin concentrations were normal. The only abnormal value was serum creatine kinase (1572 u. litre^{-1}, normal value <285 u. litre^{-1}), which was still high 2 days after operation (5 days after the marathon it was 338 u. litre^{-1}), but was within normal limits by 10 days after operation (114 u. litre^{-1}). The patient underwent ^{31}P-magnetic resonance spectroscopy (MRS) 33 h after the beginning of anaesthesia to assess the status of skeletal muscle energy metabolism.[1, 2] He was re-examined 5 months later for comparison. The patient resumed his usual training schedule 1 month after surgery.

From the MRS studies we found no evidence of altered energy metabolism of striated muscle to anaesthesia after exhaustive exercise. Variables assessing the main energy producing pathways (phosphocreatinine hydrolysis, glycolysis or aerobic oxidative phosphorylation) were similar immediately after the incident compared with 5 months later. In contrast, resting concentrations of phosphodiesters were substantially higher immediately after the incident (4.5 compared with 2.7 mmol litre^{-1}). Phosphodiesters are hypothesized to be indicators of release of membrane molecules in muscle cell damage.[3] But muscle overuse is associated with damage to the muscle contractile elements.[4] This damage to the contractile elements could also be an explanation for our phosphodiester results.

After exhaustive exercise, a general anaesthetic could cause some type of interaction between the exhausted muscles and anaesthetic agents. Importantly, significant rhabdomyolysis may occur if succinylcholine is used.

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Pain after laparoscopic cholecystectomy

Sir,—We were interested in the review article by Alexander[1] and wish to make some comments regarding local anaesthesia for pain after laparoscopic cholecystectomy.

First, Alexander[1] pointed out that analgesia tended to be given more readily during studies of pain or analgesics and that nearly all patients had received some form of intraoperative analgesia. We strongly support this view. It is difficult to compare postoperative pain when patients received various amounts of analgesics in the perioperative period. For this reason in our published study[2] no opioid or non-opioid analgesics were used for premedication or during the perioperative period. Patients received only halothane and pancuronium during anaesthesia. For postoperative analgesia, patients received metamizol on request, as was usual in our hospital, by nurses who were blinded to the treatment. Postoperative pain was measured using a VAS score. The VAS score was not used as a threshold for administrating metamizol.

Second, the timing of i.p. local anaesthetic (IPLA) is crucial, as it is for an NSAID. In the studies quoted in the review[1] and in our study,[2] IPLA was used after surgery, but in our study, in addition to that of Pasqualucci and colleagues,[3] IPLA was given before and after surgery. Administration before surgery is important for pre-emptive analgesia. Third, the site of administration is important. The quoted studies reported that IPLA was ineffective when given only into the subdiaphragmatic space. In contrast, IPLA was effective for pain relief when given onto the gallbladder bed[4] or into the subdiaphragmatic space and onto the operative area.[2, 3]

Fourth, the local anaesthetic concentration should be important. The quoted studies reported that IPLA was not effective when a low concentration of IPLA (0.15–0.25% bupivacaine) was given in contrast with those[2–4] in which IPLA was effective for pain relief when given in high concentrations (0.5% bupivacaine).

Finally, Alexander[1] concluded that local anaesthetic techniques appear to be more successful for pelvic laparoscopy than for laparoscopic cholecystectomy. We disagree. When IPLA is given at the correct time, on the right site and at the right concentration, it is also effective for pain relief after laparoscopic cholecystectomy. No side effects from IPLA have been reported. Therefore, we recommend routine administration of 0.5% plain bupivacaine 15 ml[2] or 0.5% bupivacaine 20 ml with epinephrine[3] into the subdiaphragmatic space and on the operative area before and after surgery.

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Sir,—Thank you for the opportunity to reply to Mraović and Majerić-Kogler, and to acknowledge a material addition to the evidence. In an adequate double-blind, randomized, controlled study,[1] they demonstrated the lesser need for additional analgesics and lower pain scores in those who had bupivacaine injected between the liver and diaphragm and above the hepato-duodenal ligament. Their study was not reviewed because the article was published at the same time as the review[2] was submitted.

Their method was similar to that described in an earlier article by Pasqualucci and colleagues.[3] This was primarily a study of pre-emptive analgesia and either bupivacaine or saline was sprayed above the liver and on the right subphrenic surface either before or after removal of the gallbladder, or both. Distension of the peritoneum occurred before application of local anaesthetic or saline. In those in whom bupivacaine was used at the end of intra-abdominal surgery, pain scores and ratings were lower than those in the placebo group at the end of surgery and 8 h after operation, but similar to those in the placebo group at 4 h (the time at which pain is most intense).[1, 4] Intraoperative i.v. fentanyl was used in a dose which was stated to be 15 mg kg^{-1}!

Whether or not effective local anaesthesia or systemic analgesia provides pre-emptive analgesia during continuing nociception, as distinct from requirements for effective analgesia at the time of nociception, still appears to be in dispute.

Mraović and Majerić-Kogler disagree only with my statement[2] that "local anaesthetic techniques appear more successful for pelvic laparoscopy than for, say, laparoscopic cholecystectomy". However, as they pointed out in their discussion, "six studies compared intraperitoneal bupivacaine for pain relief after laparoscopic cholecystectomy, four of which suggested that intraperitoneal bupivacaine does not reduce pain and two of which suggested that it does."

Nevertheless, the studies of Chundrigar and colleagues,[5] Mraovic and colleagues[1] and Pasqualucci and colleagues[3] suggest with increasing evidence that to which I merely alluded: that local anaesthetic techniques are more likely to be effective when the local anaesthetic is placed accurately at the site of origin of nociception in effective concentrations, rather than relying on movement or diffusion of local anaesthetic to the target area from a convenient site in the peritoneal cavity, especially when such movement is against gravity in a cavity partly filled with gas.

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Ondansetron compared with metoclopramide in the treatment of PONV

Sir,—We wish to comment on the study on postoperative nausea and vomiting (PONV) by Diemunsch and colleagues.[1] This is the largest study to date comparing ondansetron with a commonly used antiemetic in the treatment of established PONV, and showed improved outcome for patients treated with the 5-HT$_3$ antagonist. However, we were struck by the fact that even this drug, the newest and possibly most highly promoted antiemetic in the pharmacopoeia, still failed to control nausea in 56% and vomiting in 41% of patients.

A recent review in the *BMJ* by Tramer and colleagues[2] concluded that there is little information in relation to the effectiveness of intervention in established PONV, and that a 25% success rate is perhaps the best that can be achieved. The study of Diemunsch and colleagues goes someway to addressing this insufficiency in the literature and, in addition, had a greater success rate than Tramer and colleagues felt may be the best possible.

However, we feel that the study poses several questions: (1) Can we identify a group at high risk of PONV, and should we make more of an effort to do so using scoring systems such as that devised by Koivuranta and colleagues?[3] (2) If we can identify these patients, is prophylaxis effective? (3) Are there non-drug interventions that can help, such as reducing the length of the preoperative fast,[4] or the use of pre- or intraoperative i.v. fluids?[5] (4) If this study shows the best that can be achieved with single agent therapy, should future research be conducted on double or even triple agent regimens compared with other active comparators?

In a recent audit of PONV and pain in 198 sequential patients in our day-case unit, two (1%) were admitted to hospital, both as a result of vomiting. This is a small but significant number and brings to our attention the economic consequences of PONV and the distress caused by intractable vomiting and the inconvenience to the patient. It is hard to believe that we have optimized our management of PONV; perhaps more co-ordinated research will provide some answers.

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Sir,—Harper and Barker ask the question: (1) Can we identify a group at high risk of postoperative nausea and vomiting (PONV), and should we make an effort to do so using scoring systems such as that devised by Koivuranta and colleagues? Several prognostic factors are known to be associated with an increased risk of nausea and vomiting[1, 2]: female sex, previous history of PONY, use of postoperative opioids and previous history of motion sickness. In our study, we identified the prognostic factors for the absence of emetic episodes after administration of the study drug. Sex appeared to influence the antiemetic response, as 72% of male patients experienced no emetic episodes between 15 min and 24 h after drug administration compared with 48% of female patients.

Other factors influencing the antiemetic response include: history of PONV (55% of patients with a history of PONV experienced at least one emetic episode compared with 47% with no history); postoperative opioid analgesia (55% of patients who received opioid postoperative analgesics experienced at least one emetic episode compared with 45% who did not); and benzodiazepine premedication (54% of patients who received a benzodiazepine premedicant experienced at least one emetic episode compared with 40% who did not). Induction of anaesthesia with propofol had no influence on the antiemetic response, as 49% of patients who received propofol experienced at least one emetic episode compared with 50% of patients who did not.

The logistic regression analysis carried out for the absence of an emetic episode between 15 min and 24 h after drug administration showed that: (a) significant prognostic factors, adjusted for treatment, were sex, history of PONV, benzodiazepine premedication and postoperative opioid analgesia. The odds ratio (with 95% confidence intervals) for the absence of an emetic episode in the ondansetron group compared with the metoclopramide group was 2.12 (1.57–2.87), adjusted for the above mentioned prognostic factors (P=0.0001). (b) The adjusted odds ratio associated with sex indicated that males were 2.76 times more likely to experience no emetic episode than females (P=0.0006). Patients having one of the following prognostic factors experienced more frequent emetic episodes: previous history of PONV (odds ratio=0.70; P=0.0237), benzodiazepine premedication (odds ratio=0.56; P=0.0008), postoperative opioid analgesia (odds ratio=0.64; P=0.0040). No significant effect from treatment of the prognostic factors was found.

(2) If we can identify these patients, is prophylaxis effective? Yes, clinical studies confirmed that ondansetron was effective in both the prophylaxis and treatment of PONV.[3-5] Moreover, there are also other benefits from reducing PONV, such as patient global satisfaction,[6] quality of recovery and prevention of delayed recovery.[7]

(3) Are there non-drug interventions that can help, such as reducing the length of the postoperative fast, or the use of i.v. fluids before or after operation? Apart from drugs which are known to have antiemetic properties, such as lorazepam,[8] hydroxyzine[9] and propofol,[10] others factors could enhance the incidence of PONV, such as postoperative pain[11] or movement.

(4) If this study shows the best that can be achieved with simple agent therapy, should future research be conducted on double or even triple agent regimens compared with other active comparators? The incidence of PONV is approximately 60% in both the prevention and treatment studies. The number of complete responders in our treatment study does not reflect the real benefits to the patient. The non-surrogate criteria (for example, global satisfaction of the patient) reflect other benefits which are not sufficiently taken into account. These results could probably be improved with the additional use of drugs such as corticosteroids,[12] as was demonstrated in clinical studies in chemotherapy.

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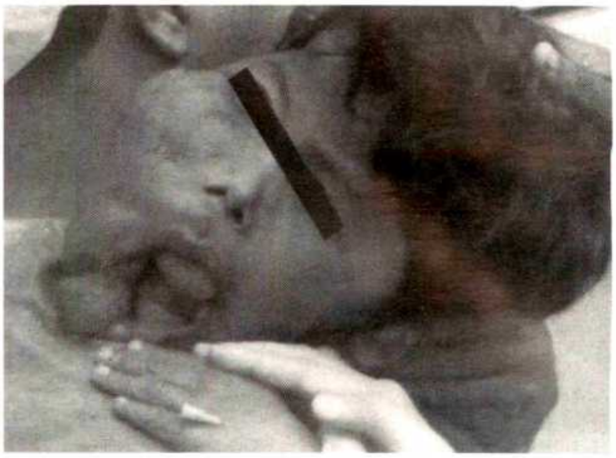

Figure 1 Patient No. 1. A 6-yr-old boy with neurofibromatosis who presented for tracheostomy and debulking of a large intraoral tumour.

Sevoflurane for difficult intubation in children

Sir,—We read with interest the case reports by Mostafa and Atherton[1] in which sevoflurane was used to induce anaesthesia in three adult patients in whom difficult tracheal intubation was anticipated. We wish to report two paediatric patients with a difficult airway where sevoflurane was used as the induction agent.

The first patient was a 6-yr-old boy with neurofibromatosis who presented for tracheostomy and debulking of a large intraoral tumour (fig. 1). He also had a 6 month' history of progressive difficulty in breathing and stridor. Inhalation induction was planned because of airway obstruction. EMLA cream was applied to both hands 1 h before induction. I.v. access was established. Anaesthesia was induced with sevoflurane in oxygen. The concentration of sevoflurane was increased gradually until an end-tidal concentration of 5.5% was achieved. Direct laryngoscopy was performed and revealed a grade III larynx which was grossly deviated to the left. The larynx was intubated uneventfully with a 5.0-mm plain Portex tube orally. Oxygen saturation was maintained at 99% throughout induction.

The second patient was a 11-yr-old girl with a fixed right temporal mandibular joint and a very receded mandible. Her inter-incisor distance was only 1 cm at full mouth opening. Fibreoptic intubation under inhalation induction was planned. I.v. access was established before induction. Anaesthesia was induced with incremental concentrations of sevoflurane in oxygen. A nasal airway was inserted via the left nostril and attached to a T-piece. When the end-tidal sevoflurane concentration reached 5.5%, the trachea was intubated with a 5.5-mm plain Portex tube nasally via the flexible fibreoptic laryngoscope. Both surgery and anaesthesia were uneventful.

A difficult airway in paediatric patients presents a challenge to anaesthetists. Inhalation induction is the technique of choice because it is often difficult to perform awake fibreoptic intubation or tracheostomy under local anaesthesia in children. We agree with Mostafa and Atherton that sevoflurane has many advantages compared with halothane in the management of the difficult airway in both children and adults. The low blood:gas solubility of sevoflurane and consequent rapid induction and rapid recovery are reassuring features in the management of difficult intubation.

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1. Mostafa SM, Atherton AMJ. Sevoflurane for difficult tracheal intubation. *British Journal of Anaesthesia* 1997; **79**: 392–393.

Caudal tramadol for postoperative analgesia in hypospadias surgery

Sir,—Prolongation of caudal anaesthesia is indeed a laudable aim. However, I have some concern with the recent article describing the use of tramadol in this role.[1] The evidence that tramadol may be effective in this regard is scanty. There is little evidence that it is safe or effective by the extradural route in adults.

We do not know the incidence of neurological damage that may be caused by this drug, and just one child with a painful or disabling neuropathy would be disastrous. Until evidence emerges of its safety and efficacy in adults, I do not believe that studies of this nature should be carried out in children.

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1. Prosser DP, Davis A, Booker PD, Murray A. Caudal tramadol for postoperative analgesia in paediatric hypospadias surgery. *British Journal of Anaesthesia* 1997; 79: 293–296.

Sir,—Thank you for the opportunity to respond to Dr Russell about our caudal tramadol study.[1]

Although we agree in principle that studies should not involve children if the relevant data can be obtained from adults, this is rarely possible. In this instance, the significant age-related differences in opioid pharmacokinetics and pharmacodynamics,[2] and vascularity, fat content and volume of the extradural space[3,4] make extrapolation of clinical data from adults to young children rather suspect. Although some initial data may be gleaned from studies of drugs injected into the lumbar extradural space in adults, our results supported the concept that data achieved in this way cannot be used to predict accurately drug pharmacodynamics after caudal injection in children. All but one of 10 adult studies and the one paediatric study published in the past decade that have examined the effects of tramadol after extradural administration have recorded encouraging results. Our findings would not have been anticipated from meta-analysis of these studies. Furthermore, for various well recognized reasons, administration of drugs into the caudal extradural space is much less common in adults than in the very young. If studies examining caudal administration of drugs in adults were required before paediatric studies could proceed, we would often have to rely solely on data from non-randomized, unblinded, uncontrolled studies carried out in developing countries.

The second point about drug safety is a thorny issue but one that is always raised at Paediatric Ethics Committee meetings when a study of a "new" drug is being reviewed. To prove the safety of any drug is almost impossible, but a thorough examination of all published (and any available unpublished) clinical and experimental evidence offers the best possible compromise between ensuring optimal safe care for our patients and advancement of our knowledge base. In this instance we were able to point out that tramadol, which has been widely available in the rest of Europe for more than 20 yr, has an exceptional safety record[5]; to the best of our knowledge no long-term adverse side effects attributable to its use have been reported.

Finally, we did not perform this study because it was possible or because we wished to write another article; we believed that there was a problem (postoperative pain in children undergoing day-case hypospadias surgery) that could be prevented or alleviated. On the basis of previously published clinical work, we hypothesized that the analgesic effect produced by bupivacaine could be usefully prolonged by the addition of tramadol. Similar studies using more conventional opioids have shown that delayed respiratory depression may, occasionally, be a problem.[6,7] Tramadol has the important and significant advantage over other commonly used opioids of having a marked lack of respiratory depressant effects.[8,9] If we had found tramadol to be clinically useful in inpatients, then we would have extended our study to day-case patients. In the light of our initial findings, we did not believe that a study extension was justifiable.

Many of these same arguments were presented and examined carefully by our Paediatric Ethics Committee before commencement of this study. One of the guiding principles used by this Committee in determining whether or not a study should be allowed to proceed is: "Children are not small adults and research should only be done in this group of patients if comparable research on adults cannot answer the same questions". We believe, as did the Ethics Committee, that this principle was strictly adhered to in the conduct of this study.

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1. Prosser DP, Davis A, Booker PD, Murray A. Caudal tramadol for postoperative analgesia in paediatric hypospadias surgery. *British Journal of Anaesthesia* 1997; 79. 293–296.
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Bair Hugger active patient warming system

Sir,—I read with interest the case report of Ayala and Coe regarding softening of tracheal tubes when used in conjunction with the Bair Hugger patient warming system.[1] As a result of their case report and subsequent study, they recommended the avoidance of uncut PVC tubes, unless adequately supported, with this warming system.

Having personally experienced a similar problem I have a simple and effective solution. This is to make a small hole in the clear plastic region of the Bair Hugger (designed to cover the patient's head) and to pass the tracheal tube through this, thus effectively removing it from the warmed environment. I have encountered no recurrence of the problem since adopting this method.

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1. Ayala JL, Coe A. Thermal softening of tracheal tubes. an unrecognised hazard of the Bair Hugger active patient warming system. *British Journal of Anaesthesia* 1997; 79: 543–545.

Inappropriate use of placebo

Sir,—Fujii, Toyooka and Tanaka compared granisetron with placebo for reduction of postoperative nausea and vomiting (PONV) in middle ear surgery.[1] First, when established treatments are available, research must be compared with existing treatments, not with placebo. I wish to know if granisetron is more or less effective than other antiemetics on offer. Second, the same authors had already proved the effectiveness of granisetron in PONV in gynaecological patients (including a placebo group).[2] Third, by withholding antiemetic therapy in the placebo group until significant morbidity from PONV had occurred represents sub-standard medical care.

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Sir,—We have already studied the efficacy of granisetron, a selective 5-hydroxytryptamine type-3 receptor antagonist, in preventing postoperative nausea and vomiting (PONV) after gynaecological surgery.[1,2] However, there is no study investigating its efficacy in preventing PONV in patients undergoing middle ear surgery. The incidence of PONV after this surgical procedure is high (62–80%) when no prophylactic antiemetic is given.[3] Therefore, we studied the efficacy of granisetron in the prevention of PONV in this population. Several investigators have previously compared the antiemetic efficacy of such new agents as ondansetron, granisetron, tropisetron and dorasetron with placebo for preventing PONV.[4-7] Similarly, we compared the efficacy of granisetron and placebo for the prevention of PONV after middle ear surgery.

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Bradycardia during rapid inhalation induction with sevoflurane in children

Sir,—In common with Sigston and colleagues,[1] we have found inhalation induction with 8% sevoflurane to be rapid and well tolerated in young children. However, the development of profound bradycardia in four children has caused us to reflect on its use. These were healthy children, aged 6 months to 2 yr, undergoing minor surgery. None was premedicated and induction was by inhalation of 8% sevoflurane and 66% nitrous oxide in oxygen, using a standard technique. In all cases the onset of bradycardia occurred during induction with no loss of airway or ventilation. One infant required treatment with atropine because of clinical evidence of a decrease in cardiac output. In the other children heart rate recovered spontaneously when the concentration of sevoflurane was reduced or we changed to using isoflurane.

In the study of Sigston and colleagues, bradycardia occurred in one child who received halothane (age unknown) but not in the sevoflurane group. It is noteworthy that all of their patients received atropine premedication. Baum, Yemmen and Baum reported no arrhythmias when comparing 8% sevoflurane with incremental sevoflurane in unpremedicated children.[2] Johannesson, Floren and Lindahl found an incidence of cardiac arrhythmias of 5% while using incremental sevoflurane in premedicated patients.[3] Otherwise, incremental induction with sevoflurane in children seems to show an increase or have little effect on heart rate.[4]

Those familiar with halothane induction in infants may admonish us for not routinely prescribing atropine where an inhalation induction is planned, if not to dry secretions and thus reduce airway complications, then to offset the myocardial depression which can accompany high concentrations of a volatile agent. The cardiovascular depression produced by sevoflurane is much less than that with halothane, but not absent. The single-handed anaesthetist, anticipating difficult i.v. cannulation, would be well advised to consider atropine premedication when planning inhalation induction with high concentrations of sevoflurane in infants.

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1. Sigston PE, Jenkins AMC, Jackson EA, Sury MRJ, Mackersie AM, Hatch DJ. Rapid inhalation induction in children: 8% sevoflurane compared with 5% halothane. *British Journal of Anaesthesia* 1997; 78: 362–365.
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Effect of temperature on diaphragmatic function

Sir,—The article by Mills and colleagues described the effect of a 5°C temperature change on the evoked compound potential in the human diaphragm.[1] They found a reduction in the EMG of approximately 60%. This is in agreement with our own findings using electromyography carried out in five children undergoing cardiac surgery under profound hypothermia. We found this effect to be almost completely reversed by edrophonium and concluded it was most likely a result of decreased production or release of acetylcholine (ACh).[2] Further experiments in dogs confirmed this effect.[3] The recent work of England added support for the view that in non-hibernating mammals, cold critically affects ACh production or release.[4]

In the past, much of our information on the effects of hypothermia has come from experiments carried out either in cold blooded animals or on tissues from rats which are genetically closely allied to hibernating animals. These species do not necessarily respond to cold in the same manner as humans and as a result conflicting findings have been reported. This article confirms the critical effect of cold in human neuromuscular conduction. If the effect of hypothermia in humans is caused by a reduction in ACh release, this also has implications for its effect on neuromuscular blocking drugs.[5]

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Sir,—We thank Professor Feldman for his comments on our results. We agree entirely that the most likely mechanism which may explain our observations is indeed impairment of production or release of acetylcholine (ACh). We regret that at the time this did not occur to us and therefore we did not perform the simple edrophonium test. Examination of the human data of Feldman[2] (quoted by Feldman) suggests that the effects of hypothermia on twitch height of arm muscles start at approximately 34.5°C. Interestingly, our data (especially during the transition from warm to cold) suggest that the effects of hypothermia on the diaphragm may be detectable at temperatures even closer to 36°C. One could speculate that there may be differences between the diaphragm and limb muscles in this respect, perhaps because the temperature within limb muscles is often hypothermic in inactive, normal subjects exposed to cold, whereas the diaphragm is not.

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BOOK REVIEWS

Review for Intensive Care Medicine. M. W. Sebastian, W. J. Fulkerson and R. L. Reed II (editors). Published by Lippincott–Raven, Philadelphia. Pp. 269.

This book is a collection of more than 700 multiple-choice questions, mainly of the true/false style, designed for candidates sitting the American Critical Care Boards. The style of questions may be unfamiliar and confusing to UK examination candidates. The reader is frequently asked to choose the most/least appropriate answer; on occasion, several of the alternatives offered would appear to be equally acceptable. I found the quality of questions variable and the lack of an index mildly irritating. Questions are based around the chapters in the book's parent text, *Intensive Care Medicine* by J. M. Rippe, and cover most aspects of critical care. The emphasis and spread of topics, not surprisingly, appears to follow the North American practice of intensive care more closely than that of the UK, with a broad scope of system-based questions.

For UK-based trainees sitting the Intensive Care Diploma there is inadequate coverage of respiratory problems; for example the subject of ARDS merits only two questions, as does weaning from mechanical ventilation. Acute renal failure is also covered by two questions, while septic shock is deserving of three. In contrast, psychiatric issues in intensive care are covered more thoroughly, with a total of 53 questions! Subjects not strictly included within the scope of intensive care in the UK, such as coronary care, are well covered, as are haematological problems. Unfortunately, most trainees from an anaesthetic background will find the section on "Procedures and techniques" basic and undemanding; it is unlikely to meet the requirements for the diploma examination.

On a more practical note, the book is soft-backed and presented in American A4 size with more than ample space for note writing. Indeed, for the sake of preserving trainee comfort and scarce natural resources, it may have been better presented in a portable pocket-sized format. The printing of the answers at the end of each chapter was not very reader friendly; I would have preferred to see the book divided into two completely separate question and answer sections.

At present there is a relative paucity of high quality intensive care revision aids. This book will therefore undoubtedly provide a useful addition to the reading material for candidates presenting for the Intensive Care Diploma. But it is unlikely to stand alone as a revision aid and will probably be found lacking in several important areas. As the number of candidates presenting for the Intensive Care Diploma increases, so probably will the availability of high quality, purpose-written revision aids. At such time, I feel this book will be judged to fall far short of the standards required for such a text.

G. Dempsey

Essential Anatomy for Anaesthetists. S. M. Black and W. A. Chambers. Published by Churchill Livingstone, New York. Pp. 198; indexed; illustrated. Price £55.00.

Some teachers who are steeped in obscure educational theories may view the acquisition of a large amount of anatomical knowledge as an unnecessary exercise for undergraduate students of medicine, let alone postgraduate students of anaesthesia. The idea is that learning facts may impede the pursuit of understanding. However, it seems difficult to see how a learner can gain an understanding of anatomy without filing away a lot of Latin names at some point in the process. The authors of this volume state that a sound knowledge of relevant anatomy remains a fundamental requirement for specialists in anaesthesia. The requirements for postgraduate examinations in anaesthesia would endorse this view. In the UK, there is a guaranteed question on anatomy in the primary FRCA examination and a question in the final examination is highly possible.

It seems that the same anatomy text will no longer serve all branches of medicine. We now have speciality-specific texts which include only those areas that are judged to be relevant to the particular specialty. This new book is divided into four chapters, covering the respiratory system, cardiovascular system, nervous system and anatomical regions of special interest to the anaesthetist. These regions of special interest include the thoracic inlet, intercostal spaces, anterior abdominal wall, axilla, antecubital fossa and the orbit. It is slightly strange to have included 18 pages on the skull and the vertebral column in the chapter on the nervous system. Why not a separate chapter? There is nothing on the mandible or the temporomandibular joint, although these are structures of some consequence in some cases of difficult intubation.

The illustrations in this book are exceptionally good. There are very clear black and white line drawings with occasional minimal use of colour—red for arteries, blue for veins and yellow for nerves (although the obturator nerve is shown as a red structure in one diagram). Muscles are coloured brown in some of the illustrations for the larynx and the orbit, but elsewhere muscles are an unobtrusive black and white and in general the illustrations are models of minimalist clarity. There are only two x-rays which are used to illustrate intra-thoracic structures and unfortunately, the key for the lateral chest x-ray is the wrong way round. The lack of other x-rays or scans is perhaps unfortunate as the clinical relevance of the study of anatomy might have been reinforced by, for example the inclusion of magnetic resonance images in the section on the vertebral column and brain, and echocardiography images in the section on the heart.

The book is printed on glossy 11 × 8.5 inch paper, so large illustrations and text can be combined with ease on a single page. The text is easy to read and anatomical names are printed in bold type in the text when the structure is the main focus of the paragraph or section. Blue coloured boxes occur throughout the book and summarize information or provide useful lists (e.g. the somatic innervation of the larynx, branches of the subclavian artery, contents of the antecubital fossa, etc.). All of these are designed to aid learning. Tracheostomy is discussed and illustrated but no other procedure receives such attention and some more clinical correlates might have been useful.

Anatomy will always be an important subject for our specialty and *Essential Anatomy for Anaesthetists* will be a very useful addition to anaesthetic department library shelves. The book is likely to prove popular with candidates for anaesthetic examinations.

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